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THE CHANGING EMPHASIS IN THE MANAGEMENT OF RENAL DISEASES

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The antigen-antibody thesis of the pathogenesis of nephritis led to the trials of nitrogen mustard, ACTH and cortisone. They proved useful in a limited group of nephrotic patients but not in nephritis. The management of renal insufficiency is directed toward the maintenance of the internal environment of the body rather than elimination. The artificial kidney and other extrarenal diffusion methods are designed to serve these functions for short periods. Hence their greatest usefulness is in patients with reversible renal injury.

THE clinical management of renal insufficiency has lagged behind the significant advances in the knowledge of the physiology of the kidney. The excretory function of this vital organ too long dominated clinical thinking to the neglect of more important considerations. Through its remarkable functions of filtration, selective resorption and excretion, the kidney holds a key position in maintaining the milieu intérieur of the body. Much fruitless effort in the classification of renal disorders overlooked the dependence of a considerable segment of the tubular system upon the efferent arterioles from the glomeruli for its nutrition.

In spite of the clearer grasp of anatomicophysiologic relationships, the common functional tests of renal capacity are notoriously inadequate. The prognosis of diseases of the kidney is therefore conspicuously insecure. Apparently mild nephritis may progress inexorably to death, while frankly uremic subjects may survive to live full spans of life without measurable renal handicap. The embryonal origin of the respective components of the nephron plays a vital role in the outcome of renal injury. The tubules take their origin from the ectoderm. Surviving the immediate onslaught of a serious injury, the tubular epithelium may regenerate in 10 to 14 days without perceptible scarring. The glomeruli are mesenchymal structures. Fibrous tissue replacement alone can result upon their destruction.[1] Dependent upon the degree of such functional encroachment, the ultimate results of glomerulonephritis will be determined.

The modern concept of the pathogenesis of nephritis has undergone radical changes. Masugi[2] produced glomerulonephritis in experimental animals by the injection of a specific anti-kidney serum. Smadel[3-5] expanded this work and by appropriate manipulations reproduced every phase of the process in the rat by injections of anti-rat-kidney serum from rabbits. The histologic changes ranged from early swelling of the intercapillary substance of the glomerular

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tuft and tubular degeneration to progressive glomerulonephritis and the generalized vascular lesions characteristic of the naturally occurring disease in man. Variations of the method do not modify the basic principles. Nephrotoxic duck serum, for example, will produce nephritis in rabbits. A more involved application of this thesis to glomerulonephritis in the human subject infers a new protein from the conjugation of streptococcal products with human kidney and the subsequent development of an antibody to the same. The interaction of the antigen (streptococcal products plus human kidney) with the antibody leads to nephritis.[6]

W. S. MIDDLETON

With the evolution of our knowledge of the pathogenesis of renal diseases, their therapy has been materially advanced. This end has been greatly enhanced by fundamental discoveries with therapeutic promise. The limitation of tubular damage from mercuric chloride by the use of BAL (2,3-dimercaptopropanol) is a conspicuous example. Longcope and Luetscher[7] recommended the prompt intramuscular injection of 300 mg. of BAL followed by two or three subsequent intramuscular injections of 150 mg. each within the first 12 hours. Their results were best when this therapy was initiated within three and a half hours of the ingestion of the heavy metal.

Furthermore, the acceptance of the plausible theory of the antigen-antibody mechanism of the pathogenesis of glomerulonephritis has revivified the clinical interest in attempts toward its control. Since streptococcal infections have been predominantly incriminated in this relation, the major attacks have been so directed. If the primary thesis be admitted, a logical target may be found in the prompt attention to streptococcal (and other bacterial) infections wherever they appear. Longcope led the advance in advising the initiation or continuance of sulfonamides in the presence of hemorrhagic nephritis attributable to streptococci. With more effective weapons in penicillin and the other antimicrobial agents now available, the objective is even more accessible than in the rheumatic state. In the prophylaxis of glomerulonephritis, penicillin should be administered in appropriate doses orally or parenterally to all patients with streptococcal infections of the upper respiratory passages, scarlet fever and erysipelas. As in rheumatic fever, the advantage accruing to such preventive measures cannot be assessed early. This circumstance is more apparent when the difficulties in establishing controls are considered.

Several tangential approaches to the problem of preventing or limiting glomerulonephritis have been pursued. Swift and Smadel[8] proved that intravenously administered saline extract of perfused rat kidney prevented the characteristic renal lesions from anti-rat-kidney rabbit serum. Extracts of rat liver have no such protective potency. Since these injections must anticipate the exposure to the nephrotoxic serum to be effective, the experiments have no clinical bearing in therapy.

Other similar leads have been suggested. Kay[6] found that rabbits exposed to roentgen rays before the injection of nephrotoxic duck serum escaped glomerular injury. Schwab et al.[9] reported that roentgen rays and nitrogen mustard inhibit the formation of precipitins for whole bovine serum and bovine serum gamma globulin in rabbits. With the resultant inhibition, injections of bovine serum globulin do not induce the characteristic vascular lesions that occur in controls. Bukantz and his associates[10] proved that nitrogen mustard administered before the injection of horse serum suppressed humoral antibody formation, cutaneous hypersensitivity and vascular lesions. In other experiments[11] on rabbits sensitized with horse serum, among a series of agents utilized, nitrogen mustard alone inhibited antibody production, the Arthus phenomenon and vascular injury. The analogy of the Shwartzman and the Arthus phenomenon to glomerulonephritis led Chasis, Goldring and Baldwin[12,13] to the therapeutic trial of nitrogen mustard in nephritic patients. Albuminuria was diminished in 25 of 28 trials. The effect on glomerular filtration was equivocal. In the edematous (nephrotic) subjects, prompt and marked diuresis occurred in 6 of 16 courses in 6 patients. Weight losses of 10 to 40 pounds

were observed. In 3 patients the edema completely disappeared. Of 8 patients treated, 2 died; 3 patients were still under treatment; the remaining 3 showed marked improvement lasting seven, one and eight months, respectively.

Taylor, Corcoran and Page[14] studied the effects of nitrogen mustard therapy in 10 patients with the nephrotic syndrome (7 with chronic glomerulonephritis, 2 with subacute or prolonged acute nephritis and 1 with amyloid nephrosis). The routine dosage of nitrogen mustard was 0.1 mg. per kilogram of body weight given intravenously for four successive days. This course was repeated after 10 or more days with careful checks on the clinical course and the blood picture. Repeated courses were afforded in 5 of 8 patients. The edema abated in 3 patients after the first course. In 2 of 3 subjects given repeated courses there was a subsidence of the edema. Two patients refused to submit to a repetition of the therapy after initial promising responses. A single patient, refractory to four courses of nitrogen mustard, succumbed while under adrenocorticotropic hormone therapy. Another of this group died of uremia some months later. The early deductions from extending experience in this area favor the trial of nitrogen mustard in carefully selected nephrotic patients, but no advantage has attended its use in glomerulonephritis and amyloid nephrosis.

THERAPY WITH ACTH AND CORTISONE

Quite naturally, adrenocorticotropic hormone and cortisone have been studied in this relation. By analogy with the rheumatic state and other conditions with a hypersensitivity background, benefit might be anticipated from their therapeutic trial in nephritis. The early enthusiasm for their usefulness in the acute hemorrhagic phase of glomerulonephritis has abated materially.[15,16] The evidence of the advantage accruing to their use under these conditions is still equivocal.[17,18] The nephrotic states respond more regularly.

A recent comparison of the results of ACTH and cortisone therapy in nephrosis[19] disclosed certain advantages for the former. Eighteen courses of cortisone were given with 10 instances of complete control of the edema, three partial successes and five failures, whereas, with ACTH, complete success attended 10 of 14 courses and there were three failures (one unaccounted). Both improved creatinine and insulin clearance. Both agents were attended early by sodium and water retention with later diuresis. The influence on proteinuria was equivocal in both cases, but later the plasma protein and albumin increased. An interesting point of divergence was observed in the impressive delayed elimination of sodium and water while on ACTH. This response is rarely noted until the interruption of cortisone. ACTH reduces the serum cholesterol. If edema is reduced by ACTH, a concomitant decrease in the sodium-retaining activity of the urinary corticoid will be registered. Metcoff, Rance and Nakasone[20] concluded that ACTH-induced diuresis is mediated by relative sodium rejection and concomitant restoration of the normal potassium transfer by the tubules. Such remissions may persist for weeks or months. Intercurrent infections precipitate prompt and often serious relapses.

Obviously these measures are directed toward the prophylaxis or the limitation of renal injury. Failing of these objectives, the patient with serious renal disease faces the possibility, imminent or remote, of acute renal insufficiency. Regardless of the basic etiology and pathology, certain broad principles control the therapeutic attack and in some measure the prognosis. In planning the approach, several questions present themselves, viz.: Is the underlying renal condition reversible, irreversible or an acute exacerbation of an essentially irreversible disease? Indeed, in the absence of a definite history, the differential diagnosis between acute glomerulonephritis and the lower nephron nephrosis may rest on such details as the greater albuminuria and hematuria and the higher incidence of edema and arterial hypertension in the former. Oliguria or anuria, on a nonobstructive basis, leads to acute renal insufficiency with its concomitant threats to the heart and the circulatory system as well. Nor may the clinician depend implicitly on laboratory determinations to establish the clinical status of the patient.

Perhaps the most important clinical contribution, in the impressive volume of research on

renal disorders, has been the significant shifting of the attention from the retention of protein waste products in these patients to more important biochemical derangements. With injury to the glomerular filter and to the tubular resorptive and excretory mechanism, profound disturbances in water balance, acid-base equilibrium and electrolyte functions may be anticipated. Hence, observations of the body weight will supplement recording of the intake and the output of fluids. As important as are the determinations of the nonprotein (or the urea) nitrogen and creatinine of the blood, modern clinical medicine requires frequent studies of the sodium, potassium, calcium and chloride content and the carbon dioxide-combining power of the blood to anticipate or to meet serious deviations from normal. Odel[21] recommended daily studies of the urea (or nonprotein) nitrogen, chlorides and carbon dioxide-combining power along with intake-output figures. The hemoglobin, erythrocytes and serum protein, in his opinion, should be established every two days. Especial attention should be directed to the circulatory status. Sharp accession of arterial hypertension may anticipate serious hypertensive encephalopathy with its train of dangerous manifestations.

Bull and Jockes[22] divided the patients with anuric uremia into two groups for therapy, namely, (1) those whose kidneys were capable of excreting water, but unable to maintain the normal milieu intérieur, and (2) those with negligible capacity for the excretion of water. Excluding from the immediate consideration the special indications for fluid in patients with lower nephron nephrosis, there is still a sharp division of opinion on the matter of fluid intake for patients with acute renal insufficiency. Schemm and Hurst,[23] attacking the continued adherence to the Starling theory of edema, stressed the importance of the electrolyte factor in nephritic edema. They prefer the term "brine-logged" to "waterlogged." In their approach, dehydration may be of two types: (1) "salt-plus-water" loss, as in vomiting, and (2) "true" dehydration in which "plain water" loss is related in the inadequacy of fluids to meet the requirements for temperature regulation and urine formation. On these basic premises, they concluded that the former group needed sodium chloride and water, and the latter only water to correct the fault.

In general, for elimination of sodium and solid wastes and the correction of acid-base inequilibrium, these workers maintained that, even though impaired, the kidneys were the "ultimate guardians of the internal environment" and would best regulate the volume and composition of the same if afforded adequate water. Theoretically, the greater the damage to the kidneys, the greater would be the requirement of fluid intake, but practically they fixed the minimum as the amount necessary to correct the pre-existing "plain water" deficit plus the daily vapor loss. Arbitrarily, the amounts of urinary water to eliminate the solids were placed as follows:

Specific gravity of urine	*Minimum output*	*Optimum output*
1.032	500 cc.	1500 cc.
1.015	1600 cc.	2500 cc.
1.010	2000 cc.	3000 cc.

In the opinion of Schemm and Hurst, with due allowance for water vapor loss, "plain water" deficit and urine water need, many nephritic patients have an immediate fluid requirement of 6000 cc. daily for two days, and 4000 cc. daily thereafter. Full consideration must be given to the electrolyte pattern under such a regimen. On the other hand, Lattimer[24] insists that a notice be placed on the beds of all acute anuric patients, "Total fluids limited to 1000 to 1300 cc. in 24 hours." Other workers[1, 22] maintain that there is no basis for pushing fluids in the anuric subject, and recommend a limitation of fluid intake to the extrarenal loss by respiration and insensible perspiration. An average of 800 to 1000 cc. per day should meet this requirement unless there is sweating, vomiting or diarrhea. Attention must be paid to the state of hydration.

Hemoconcentration not only vitiates the determinations of certain blood constituents, but also materially increases the toxemia of renal insufficiency. Parenteral fluids are indicated under these circumstances. Azotemia, which has so long occupied a predominant place as an index of renal insufficiency, is profoundly influenced by dehydration. Its occurrence and especially its progressive increase, regardless of the

basic mechanism, must be frontally met. If the oral route is denied, 5 per cent glucose in distilled water should be administered in appropriate amounts. The acidosis of renal insufficiency has received increasing attention in recent years. In this form of disturbed acid-base equilibrium, Elkinton, Squires and Singer[25] adduced evidence favoring the whole blood "buffer base" determinations over the conventional carbon dioxide content which fails to account for the protein anion in the erythrocytes and the plasma. Furthermore, their studies indicated the importance of the shift of sodium intracellularly, the excretion of sodium and the balance of chlorides in determining the ultimate effect of alkali administration on acidosis. Peters and his associates,[26] in studies of acidosis of nephritis, concluded that phosphate increase is relatively insignificant in this direction. Furthermore, sulfates and organic acids are less important than was suspected. These workers disclosed marked variations in the base and chlorides by reason of the renal inability to maintain balance.

A true bicarbonate insufficiency actually exists in many instances of acute renal insufficiency. Since the several factors involved are unpredictable, the dosage of alkalies can only be approximated by their effect. Sodium bicarbonate may be given by mouth or rectum in doses of 4 gm. every three hours. Infusions of 1.2 per cent sodium bicarbonate solution in distilled water may supplement or replace the oral route. Snapper[1] objected to sixth-molar sodium lactate because of the large amount of fluid required to meet the objective. He recommended 5 per cent sodium bicarbonate solution intravenously. Using the carbon dioxide-combining power as a therapeutic index, Lattimer[24] recommended that 70 to 90 volumes per cent be the objective. Compromising the extremes of dosage and the target of carbon dioxide-combining power, oral sodium bicarbonate or 2 to 3 per cent sodium bicarbonate solution intravenously in amounts necessary to restore and maintain normal acid-base equilibrium is advised in the acidosis of renal insufficiency.

The electrolyte imbalance of serious renal damage is receiving increasing clinical notice. In no other relation is the milieu intérieur more seriously impaired in renal insufficiency. Sodium retention results from an incapacity of the glomerulus to filter this cation, or from an indiscriminate resorption by the damaged tubular system. Beyond the renal level, Elkinton and his fellow workers[25] established a singular intracellular cation exchange in renal acidosis. From 29 to 108 per cent of the sodium administered as sodium bicarbonate to 8 patients with severe renal insufficiency entered into the intracellular phase. The potassium of the cells passed into the extracellular compartment in considerable amounts. As Schemm and Hurst[23] maintained, edematous patients are "brinelogged" rather than "waterlogged."

SODIUM RESTRICTION

The therapeutic indication for sodium restriction is clear. Limitations of sodium intake to 500 to 800 mg. a day are easily accomplished. At times it may be necessary to attain a level of 200 mg. a day, but such extremities are maintained at the serious risk of sodium deficiency. Substitutes for table salt must observe the basic indication for the limitation of sodium. The utilization of cation exchange resins for the purpose of increasing the palatability of the diet has a very limited application in this relation. Where these agents are used, due attention should be given to the electrolyte levels of the blood, for dangerous deficiencies may appear insidiously.

Potassium function in renal insufficiency has been increasingly studied in recent years. In experimental ureteral ligation or nephrectomy, Hoff, Smith and Winkler[27] noted eventual cardiac arrest from potassium intoxication. These workers[28] established arbitrary values for the electrocardiographic effects of increasing blood concentrations of potassium; at 5 to 7 mEq. per liter, altered T waves appeared; 8 to 10 mEq., depressed S-T segment; 10 mEq., intraventricular block; 9 to 11 mEq., P waves disappeared, and 14 to 16 mEq., cardiac arrest occurred. These data have enhanced usefulness if a flame photometer is not available for routine determinations of blood potassium levels.

Potassium deficiency may occur in renal insufficiency, dependent on decreased intake from anorexia and vomiting and increased loss through the catabolism of proteins and the fail-

ure of tubular function. Alkalosis and dehydration favor this serious imbalance. If diabetes complicates the picture, the notorious loss of potassium under insulin therapy must ever be borne in mind. Furthermore, the administration of desoxycorticosterone, adrenocorticotropic hormone or cortisone may seriously jeopardize the potassium reserve. Muscular weakness, stupor and convulsions may attend this disturbance. These circumstances require diametrically opposed approaches. Limitation and elimination of potassium are indicated in hyperkalemia. The situation may be so desperate as to require artificial dialysis. Hypokalemia may be more directly resolved. If the deficit of potassium is recent and of minor degree, 3 gm. of potassium chloride by mouth daily will suffice. If the condition is emergent or if the oral route is denied, 3 to 6 gm. of potassium chloride in 0.1 to 0.2 per cent solution of 5 per cent glucose or normal saline may be given intravenously.[29] Of course, the renal incapacity renders the administration of potassium hazardous. Hence, every precaution of frequent serum potassium determinations and electrocardiographic tracings must be invoked in its control.

From a position of supreme importance in renal physiology, the chlorides passed almost to a point of clinical neglect. By salt-loading and depletion studies in man, Wiggins, Manry, Lyons and Pitts[30] established a marked difference in the capacity of the normal and the potentially edematous subject to adjust tubular absorption of salt to the intake. By simple but unexplained shifts in this mechanism, the normal subject avoids edema on salt-loading. However, the blood chlorides are commonly reduced in renal insufficiency. Thorn, Koepf and Clinton[31] reported 2 nephritic patients with extreme collapse from hemoconcentration, dehydration and hypochloremia, whose condition closely paralleled adrenocortical insufficiency.

The "low salt syndrome" has been carefully studied by Schroeder,[32] who questions whether it can develop in individuals with normal kidneys. Whatever may be the ultimate answer to this problem, the "low salt syndrome" is also encountered in cardiac and cirrhotic patients on low sodium chloride intake, whose chlorides are further depleted by vomiting, diarrhea or diuresis induced by mercurials. Weight gain, oliguria, weakness, prostration, drowsiness, nausea, vomiting, abdominal and muscular cramps and steadily mounting nonprotein nitrogen in the blood characterize this condition. Coma and death may ensue. Perhaps the illusionary nitrogen retention may be charged with the responsibility for misdirecting the clinical attack. Likewise, salt depletion rather than the mercurial diuretics per se may be found culpable in certain deaths ordinarily attributed to the latter.

If the organic mercurials are used in combination with low sodium diets, or vice versa, blood urea determinations should be made every other day.[33] Fortunately, if the causal relationship of salt depletion to this startling syndrome is borne in mind and recognized, its correction and control are usually quite simple. After the initiation of symptoms, physiologic saline solution does not suffice to meet the issue promptly. Snapper[1] recommended 4 per cent, and Schroeder[32] 5 to 6 per cent sodium chloride solution slowly administered intravenously to meet this emergency. Under ordinary conditions the chloride deficiency may be met and balance be maintained by sufficient oral sodium chloride to insure the normal urinary excretion of 5 to 6 gm. a day.[33] Muscle cramp and actual tetany may result from calcium deficiency in renal insufficiency. Oral or parenteral calcium will promptly correct the fault.

DIETARY REQUIREMENTS

Perhaps no element in the management of renal insufficiency has been fraught with sharper division of opinion than the dietary requirements. Addis[34] held tenaciously to the thesis of an increased functional burden to the damaged kidneys by every increment of protein, whose ultimate products were so cleared from the body. On experimental and clinical grounds, he prescribed diets containing as little as 0.2 gm. of protein per kilogram of body weight for the patient with acute hemorrhagic nephritis. From this point, he advocated very gradual advances to 0.75 gm. per kilogram of body weight. In a fundamental study of the problem of the chronic nephritic subject, Keutmann and McCann[35] found no measurable handicap to pa-

tients receiving from 40 to 200 gm. of protein a day. The general clinical improvement of patients on the high protein diets counterbalanced the slight increases in proteinuria and transitory azotemia occasioned by the liberal protein ingestion.

In general, students of the subject are agreed that a high carbohydrate, low protein diet is indicated in frank renal insufficiency. Borst[36] adduced evidence that a high carbohydrate intake, with fat to bring the caloric value just below actual requirement, would materially decrease protein catabolism, and, by the same token, potassium release from the cells and nitrogen excretion. Bull and Jockes[22] advised the following solution as a continuous nasal drip: glucose 400 gm., peanut oil 100 gm., and water 1 liter with acacia, q.s. to emulsify (vitamin supplement optional). All vomitus is collected, filtered through lint and returned to the stomach to avoid the loss of electrolytes.

Among the most inviting therapeutic objectives in renal insufficiency, especially if attendant upon oliguria or suppression, is the induction of diuresis. Natural as may be this design, there are many obstacles to its accomplishment. Hot fomentations or diathermy to the flanks may be useful. Procaine block of the lower two thoracic and the upper two lumbar sympathetic ganglia[37] may give dramatic diuresis if spasm of the afferent arterioles to the glomeruli is responsible for the anuria. This procedure may be repeated within the 24 hour period, if unsuccessful at first. Renal decapsulation has been recommended for urinary suppression on the theory that the anuria results from increased intracapsular (renal) pressure. Culpepper and Findley[38] have reviewed the literature critically and have concluded that the evidence in its support is equivocal. Furthermore, they proposed that unilateral decapsulation be employed to attempt to establish both the pathogenesis of the anuria and a clear judgment of possible indications for operation. Presently the matter stands sub judice.

Furthermore, irritant diuretics are patently contraindicated in the presence of acute reactions when they may actually be harmful. Lashmet[39] paved the way for a revolutionary change in the approach to this problem. In the presence of edema, the nephritic patient is still capable of excreting water and chlorides. Yet sodium chloride increases the edema, while hydrochloric acid and ammonium chloride decrease it. In a word, the reaction is more important than the chloride content. Applying this principle, Lashmet advised a low protein, salt-poor, neutral ash diet with forced fluids and acid-producing salts.

Interestingly, in his graduation thesis from Pennsylvania (1798), Philip Prioleau[40] anticipated the modern concept in the following significant observation: "From the oxigenated muriatic acid, in every instance in which it was exhibited, proving powerfully diuretic, I flattered myself that it would be found an invaluable medicine in dropsy." His further studies confirmed its value in congestive heart failure. Indeed, its control of edema and dyspnea upon marked diuresis led him to consider "oxigenated muriatic acid" more efficacious than digitalis under these circumstances. The kidneys must possess a reasonable margin of functional reserve to justify the use of acidifying salts for diuresis. This situation obtains in the nephrotic states; but in the renal insufficiency of nephritis, ammonium chloride, ammonium nitrate and calcium chloride would be administered very cautiously. Close observations of the acid-base equilibrium, the electrolyte balance and nonprotein nitrogen levels must be pursued to avoid disaster. Hypertonic glucose solutions have had support for their diuretic effect in certain quarters, but their use is decreasing. Sucrose is interdicted by its serious nephrotoxic potentiality. Water is still a good diuretic and, in chronic renal insufficiency, amounts sufficient to insure a urinary output of 2500 to 3000 cc. are justified in meeting advancing azotemia.

Arterial hypertension is the common result of increasing glomerular damage. Indeed to a point this increased intravascular pressure is compensatory to insure a maximal efficiency of filtration. Earle and his associates[41] determined a marked reduction in the filtration rate and the filtration fraction with less marked decrease in the excretory and resorptive functions in acute glomerulonephritis. The compensatory function of arterial hypertension may shortly exceed physiologic bounds and, with coincidental changes in the general vascular bed, a vicious

circle is initiated that interacts to the progression of the basic glomerular handicap. Hypertensive encephalopathy is one of the most devastating manifestations of this condition. While it occurs more commonly in nephrosclerosis, it is not infrequent in glomerulonephritis.

The neurologic expressions of hypertensive encephalopathy may range from headache, tinnitus and amblyopia to paresthesias, paresis, paralysis, convulsions, coma and death. The more serious evidences of this condition constitute a major medical emergency. Murphy,[42] from an extended experience, recommended 20 cc. of a 20 per cent magnesium sulfate solution intravenously, to be repeated every four hours or until the convulsions are controlled. Normally the blood level of magnesium is 1.5 to 3 mEq. per liter. For therapeutic effect, this level must be raised to 5 mEq. per liter. The intravenous administration of magnesium is not without danger, especially in renal insufficiency. One of the most powerful depressants known to science, magnesium should never be given by this route without preparing antidotal calcium gluconate or chloride in a convenient syringe.

In our experience, spinal puncture may frequently relieve the more urgent symptoms of hypertensive encephalopathy. Venesection has a very limited place in this relation, and hypertonic glucose solution at times gives a rebound reaction that aggravates rather than relieves the situation. Although there are theoretical objections to the use of tetraethylammonium or similar compounds for these indications, certain splendid results commend the following procedure: Since the arterial blood pressure has usually risen sharply with the clinical manifestations of this crisis, 200 mg. of ETAMON® is given slowly intravenously. The objective is the attainment of the precritical level of blood pressure. Where this result is promptly accomplished, relatively small additional doses of etamon are required to maintain the advantage. It is unusual to encounter a successful effect after an initial failure.

Cardiac failure after a long period of arterial hypertension, as seen in nephrosclerosis and chronic glomerulonephritis, is commonplace. Its management requires the same careful planning of physical activity, low sodium, adequate fluid intake and digitalis that the failing heart of any other origin demands. Special indications will differ in no wise. On the other hand, heart failure in acute nephritis demands especial attention. Davies,[43] by cardiac catheterization, proved that, although the cardiac output and stroke output of patients with acute glomerulonephritis remained normal, the venous pressure was elevated. The lack of correlation among a number of factors, including venous pressure, arterial pressure, electrocardiographic changes, circulation time and edema, raised a serious question as to the primary cardiac responsibility. The absence of serious myocardial change on histologic study gave support to Davies' contention. In his opinion, the elevated venous pressure, edema, cardiac enlargement and even pulmonary edema of acute nephritis may all reflect the hydremia of water retention. If this position be sustained in any part, the therapeutic indication for sodium restriction and the avoidance of excessive fluids intravenously are clear. Beyond this, digitalis, oxygen and small transfusions may have their special applications to the needs of the individual patient.

SUBSTITUTE DIALYZING MECHANISM

Of all measures designed to meet the specific requirements of renal insufficiency, the most attractive thesis would substitute a dialyzing mechanism temporarily for the handicapped kidney. In 1913 Abel, Rowntree and Turner[44,45] proposed "vividiffusion" to supplement the excretory function of disordered kidneys. Using hirudin as the anticoagulant, a closed system of celloidin or other dialyzing membrane carried the blood from the artery of the animal through a saline bath back to the body. Renewed interest arose from Kolff's vastly improved artificial kidney[46] which afforded a dialyzing area of 20,000 square centimeters, among other advantages. Further improvements have been made by Murray and his co-workers[47] and Alwall[48] and Owsley and Kirwin.[49] Merrill, Smith, Callahan and Thorn[50] reported 60 runs on 43 patients in an improved Kolff apparatus. Their control of the tonicity of the fluid in the dialyzing bath, elimination of clotting, hemolysis and pyrogenic reactions constitute major stages in the technical

improvement of the artificial kidney. All students of this phase of the subject have reported the ready diffusion of certain waste products, as urea, creatinine and uric acid from the circulating blood, into the dialyzing bath, but important electrolytes are subject to the same forces and hence may be lost to the body in serious proportions. Furthermore, observations of the results of the artificial kidney in uremic patients have confirmed the lack of correlation between the level of the nonprotein nitrogen and the clinical status. Sharp declines in the nonprotein nitrogen may be unattended by clinical improvement. Potassium has an especially important place in renal insufficiency, and many of its serious manifestations, as stated before, arise from hyperkalemia. By appropriate chemical adjustment of the dialyzing bath, imbalance in the circulating electrolytes of the blood may be controlled within reasonable limits.

To date the artificial kidney is a complex apparatus available to a few medical centers under the supervision of a well coordinated team. There is no prospect of an early simplification of the complexity of its manipulation and control. Its maintenance and operation are expensive. Furthermore, its limitations are now well defined. Simply stated, the artificial kidney may prove useful in any instance of renal insufficiency where the basis is temporary and reversible. Merrill[51] concluded that this measure should be considered an adjunct to conservative treatment in prolonged anuria. By common consent, its greatest application will be found in patients with lower nephron syndrome from whatever cause, where support for 10 to 12 days by artificial dialysis may find tubular regeneration far enough advanced to resume normal function. The indications in acute and chronic nephritis are less clearly defined, and the results quite unconvincing. Illusionary advantages under these conditions are frequently limited to temporary declines in the levels of the nonprotein nitrogen of the blood. Some of the dramatic results from the use of the artificial kidney attend the control of hyperkalemia and pulmonary edema in acute renal insufficiency. This apparatus furthermore affords an excellent instrument for physiologic studies that has not yet been exploited.

Schemm and Hurst[23] maintained: "No dialysis method yet devised can compare in efficiency with even badly impaired kidneys that are supplied with enough urine water." Grollman and associates, in a series of important contributions,[52-55] have taken a very conservative position relative to the management of acute renal insufficiency. By careful control of the electrolyte and water balance, they recorded a mortality of 15 per cent among 27 patients with severe acute renal failure as contrasted with the conventional mortality figures of 80 to 90 per cent. Using nephrectomized dogs as the standard test animals, these workers sustained life and electrolyte balance better by intermittent peritoneal lavage, with due attention to the correction of the chemical dislocations of the blood, than with the artificial kidney. Ganter[56] first suggested this method of dialysis. The peritoneum affords a dialyzing surface of about 22,000 square centimeters, an area roughly comparable to the glomerular filter.[57] Its simplicity and safety render peritoneal lavage more available and more practical than the artificial kidney. The Texas group[54,55] advised intermittent peritoneal lavage every two hours. Utilizing a polyethylene tube, the perfusion fluid—composed of sodium chloride 5.77 gm., calcium chloride 0.2 gm., magnesium chloride 0.05 gm., potassium chloride 0.20 gm. and sodium bicarbonate 3.00 gm. per liter—is injected and withdrawn through the same opening. Minor adjustments in the composition of the perfusing fluid will be dictated by changes in the blood levels of the electrolytes. Reid[58] cautioned that these alterations may occur very precipitously. Furthermore, anemia usually occurs and must be met by transfusion.

Odel, Ferris and Power,[57] after reviewing the literature, recommended conservative measures before the initiation of peritoneal lavage. They limit its indications to a reversible basis for anuria. In addition, they would require evidence of the inadequacy or failure of the simple medical support for several days before resorting to artificial means. Snapper[1] would discontinue peritoneal lavage when the polymorphonuclear neutrophils become numerous in the returned dialyzing fluid. By experimental studies on nephrectomized dogs, Seligman, Frank and Fine[59] concluded that this method was 50 to 75

per cent as effective as the normal kidney.

Vermooten and Hare[60] recommended continuous gastric lavage for the treatment of uremia. By this procedure in prostatic patients, they encountered gratifying falls in blood urea within seven hours, and marked clinical improvement of all evidences of renal insufficiency in 48 to 72 hours. In 3 patients with nephritis (1 with renal periarteritis), no sustained advantage accrued to this method of treatment. Goudsmit[61] utilized forced intestinal drainage for the extrarenal elimination of protein waste products. Introducing a Miller-Abbott tube into the jejunum and then blocking the intestines with a balloon at its termination, hypertonic sodium sulfate was given into the duodenum through a second lumen. In 3 normal control subjects, the average amount of fluid removed was 655 cc. per hour with a urea concentration 93 per cent of the blood. In 2 patients with renal insufficiency, the hourly fluid removed averaged 399 cc. per hour, and the urea concentration 75 per cent of the blood level. Since the total removal of 10 gm. and 4 gm. of urea, respectively, in over seven hours, did not affect the blood level, Goudsmit recommended longer periods of lavage.

White and Harkins[62] employed intestinal lavage in the control of experimental uremia. In nephrectomized dogs, intestinal loops were irrigated with hypertonic solutions with the removal of large amounts of urea but without appreciable prolongation of life. Bernstein and his co-workers,[63] employing a double lumen gastric tube by the nasal route, studied the effects of pergastric intestinal perfusion in uremic patients. The irrigating fluid contained 147 (or 142) mEq. of sodium, 5 (or 10) of potassium, 103 of chlorides, 52 of bicarbonate and 3 of magnesium together with 20 gm. of glucose per liter. The optimal rate of flow was 2.5 liters per hour. They confirmed the ready excretion of urea and nonprotein nitrogen into the intestinal perfusion, but found only a slight loss into the gastric washings. In a period of 8 to 28 hours, the serum nonprotein nitrogen fell an average of 59 mg. per 100 cc. and the calculated urea clearance of this method ranged as high as 21 cc. per minute. Significantly, even with the protection of potassium in the perfusing fluid, serious losses of this element occurred. Water, sodium, chlorides and bicarbonate were retained in all subjects. Elevation of serum sodium and edema must be anticipated and met by careful observation and corrective measures. Two of 7 patients treated by this method of intestinal perfusion showed marked clinical improvement. Even where ultimately unsuccessful, death from renal insufficiency may be deferred. The grace period gained recommends its consideration in the presence of uremia from a reversible cause.

Exsanguination transfusions have been more extensively utilized in the treatment of renal insufficiency abroad than in this country. Their technic is involved. An exchange of 7 to 8 liters of normal blood for that of the patient is accomplished in six hours. Such a procedure results in an estimated replacement of 80 per cent of the recipient's original blood. Snapper[1] advised the administration of calcium gluconate to prevent tetany which may result from the fixation of the blood calcium by the citrate of the transfusion.

Since these methods are most promising in the management of renal insufficiency arising from a reversible injury to the kidneys, the lower nephron nephrosis may be taken as a disease type for their application. Minami[64] first related renal damage and urinary suppression to muscle necrosis. Bywaters and Beall[65] adduced further support for this explanation of the crush syndrome. Renal anoxia[66] and ischemia[67] have been invoked as directly exciting mechanisms. Van Slyke and his co-workers,[68] in studies of experimental animals in shock, established a virtual cessation of blood flow through the kidneys. Three phases of response were observed: (1) reduced renal function without damage to the nephrons; (2) reversible damage to the nephrons, and (3) irreversible damage to nephrons, if the renal arteries were clamped for more than four hours. Apparently the inability of the renal parenchyma to modify its oxygen demand in the presence of decreased supply determines the disproportional irreversible changes.

Lucké[69] recognized the least common denomination of a number of serious renal injuries in the histologic changes in the lower nephron. He listed as causes of this renal lesion, muscle trauma, nontraumatic muscular ische-

mia, burns, transfusions with incompatible blood, heat stroke, blackwater fever, toxemias of pregnancy, uteroplacental damage, alkalosis, sulfonamide intoxication and certain other poisonings. French[70] proposed the designation "glomerulonephrosis" by reason of the presence of demonstrable glomerular changes.

The clinical picture of the lower nephron nephrosis follows a common pattern. As a type following a crushing injury, the patient may react favorably to the initial supportive measures. Shock is controlled by the usual methods and the early prospect is bright. Vomiting may be the first disquieting symptom after the initial reaction. Shortly the urinary output is reduced and oliguria may give way to complete suppression. The urine may be dark in color in the stage of oliguria. Chemical reactions for hemoglobin are positive, dependent on the muscle hemoglobin or myoglobin. Proteinuria is characteristic. Granular casts abound in the urine. With the progressive oliguria, azotemia advances. Later the alkali reserve will fall and the serum potassium rise significantly. Slight to moderate arterial hypertension is the rule. Edema of the subcutaneous tissues is common, but it rarely takes the nephritic distribution. Pulmonary edema may dangerously complicate the process. In the more serious instances of the crush syndrome, lassitude, drowsiness and coma may presage death. Lucké[69] estimated that the mortality of lower nephron nephrosis approximates 90 per cent. Bywaters and his associates[71] found the first week after trauma the critical stage, and determined that recovery was the rule if the injured patient lived through the eighth or the ninth day. The recuperability of the tubular epithelium determines recovery of the survivors. With its regeneration comes a sudden change in the water balance, and the marked diuresis creates a new crisis.

The therapeutic indications in the treatment of the lower nephron nephrosis follow these stages of disturbed renal physiology naturally. Early the fluid intake should be limited to the combined total of the insensible perspiration and the urine (800 to 1000 cc.). Proper adjustment for fluid losses by emesis and diarrhea must be made. Pulmonary edema and potassium intoxication may be determining factors in the prognosis. Simple measures of fluid restriction and dietary limitation (to 100 gm. of glucose daily) will favor spontaneous recovery. Murphy[42] would resort to the support of the artificial kidney only after eight days of conservative therapy without restoration of renal function. The same rule may be applied to peritoneal and gastrointestinal perfusion. Pulmonary edema and hyperkalemia may respond brilliantly to these measures. Decapsulation stands sub judice.[38]

With the period of diuresis comes the necessity for prompt, intelligent therapy. Strauss[72] has indicated the requirements for complete physiologic restitution by close attention to the electrolytes. Hypochloremia, hypokalemia and hypocalcemia must be directly met. The great loss of fluid upon diuresis must be compensated by high intake. Anemia is common and may require transfusions for its correction. Importantly, recovery from lower nephron nephrosis is usually physiologically as well as anatomically complete.

In summary, the most significant objective in the field of renal diseases lies in their prophylaxis. Promising bridgeheads have been made in this direction, but the advance has been stayed by a lack of clear definition of the pathogenesis on one hand and the equivocal results of bactericidal or bacteriostatic agents on the other. The employment of nitrogen mustard, ACTH and cortisone in attempting to modify the course of nephritis and nephrosis, sound though the initiating tenets may have been, is still in an experimental phase. Until the indications and probable effects are more clearly defined, their use should be confined to the well controlled, completely equipped clinic.

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PULMONARY AND CUTANEOUS DISEASES CAUSED BY BERYLLIUM COMPOUNDS

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Beryllium is a metal that in recent years has been found to have important industrial uses. Compounds of the metal have the ability to produce acute pneumonitis, as well as chronic disabling pulmonary disease and acute or chronic inflammation of the skin. The diagnosis of disease caused by beryllium depends on proof of exposure to beryllium and on the presence of roentgenographic and other clinical signs of such disease.

BERYLLIUM is a light, hard metal which has peculiar properties that are of great interest to the Atomic Energy Commission and to the makers of neon tubes and of certain copper alloys used in the manufacture of precision and fatigue-resistant instruments. It is also used in radio tubes and as the metal windows on x-ray tubes. Beryllium, being an element of atomic number 4, is quite pervious to roentgen rays, unlike the heavier metals such as lead or gold, and one of its chief civilian uses is in the fabrication of x-ray tube windows.

Beryllium was a laboratory curiosity until about 1930, when it was discovered that beryllium oxide has the property of imparting bright fluorescence to mixtures of several compounds, including silica and oxides of zinc and manganese. Shortly thereafter it was put to practical use with the invention of the fluorescent light tube. Beryllium oxide was incorporated into powders that were used to line fluorescent light tubes like those we see today in many department stores, factories and homes.

The medical case against beryllium began near Cleveland, Ohio, in two industrial plants that were extracting beryllium from its ore. It was noted that several employees had an acute dermatitis and, more seriously, a peculiar kind of acute pneumonitis. This pneumonitis was recognized as being unique to the beryllium reduction industry, and at first it was assumed that the fluoride which is an essential part of one of the reduction processes was the causative factor.

Meanwhile, at a plant in Massachusetts, the beryllium oxide prepared in the Cleveland plants was being used for the manufacture of fluorescent tubes. Some of the employees in this plant developed a chronic granulomatous pulmonary disease which at first was thought to be Boeck's sarcoid. Gradually, however, it became apparent that there was a much higher incidence of this disease in the plant population than of Boeck's sarcoid in the geographic area around the plant.

The disease developed among these employees with considerable regularity and severity until about 1942, when, because of the Atomic Energy Commission's demands for beryllium, the phosphor that had required 12 per cent beryllium oxide was reduced to only 4 per cent beryllium oxide.* Employees who were hired after the reduction in the percentage of beryl-

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*More recently, a phosphor has been developed that contains no beryllium compounds, and fluorescent tubes being manufactured today are being coated with the beryllium-free fluorescent powders.

lium oxide did not develop the disease. Some persons who had been exposed to the phosphor that contained 12 per cent beryllium oxide became ill with this chronic pulmonary disease even after significant exposure had been precluded for several years, and there are records of the onset of chronic pulmonary berylliosis as long as seven years after exposure.

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In addition to the concomitant appearance of these two kinds of pneumonitis and the acute dermatitis, another condition became apparent which ultimately led to the proof that beryllium was the pathogenic factor. This was the occurrence of cutaneous granulomas in persons in whom beryllium-containing fluorescent powders had become imbedded in an abrasion or a laceration of the skin. These granulomas were identical with those seen in the lungs of persons with chronic granulomatosis. About 50 such cases of granuloma caused by beryllium-containing phosphor are known, and some of these have been reported. One case was that of a young woman who was cutting pure metallic beryllium for use in the manufacture of x-ray tube windows. The cutting wheel abraded her finger, and within a few months she developed typical cutaneous beryllium granuloma. These granulomas do not occur in the absence of beryllium, even in wounds contaminated with powders which quite closely resemble the beryllium-containing phosphor.

The majority of cases of acute beryllium pneumonitis have occurred in the area around Cleveland, Ohio, in persons who had been exposed to soluble compounds of beryllium. A few cases have been reported from other areas; in these, the persons had been exposed only to fumes or dust of beryllium oxide. In the beryllium reduction plants, the men who have developed acute beryllium pneumonitis often have been found to be those who had been employed there for a relatively short period of time, and usually they had been working in an area where they were exposed to mists or sprays that contained beryllium fluoride or, more rarely, beryllium sulfate. There have been a few cases in which the persons had been exposed only to the beryllium oxide, a special feature in such cases generally being that the oxide had been either freshly prepared or freshly heated. Even though they are insoluble, these freshly heated or prepared compounds seem to produce a tissue reaction more readily than do the dusts of insoluble compounds formed weeks or months previously. This is analogous to the idea that freshly fractured grains of silica are more likely to produce silicosis than is a dust composed of particles that were formed some time previously; in other words, over a period of time a reorganization of the molecules within a particle takes place so that its potential effect on tissues diminishes.

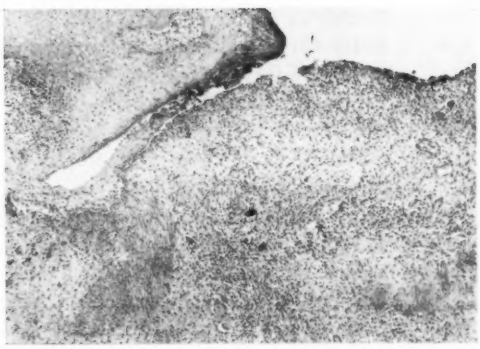
Acute beryllium pneumonitis begins with a dry, irritating cough that occasionally is productive of a small amount of blood-tinged sputum. There is an extreme degree of exertional dyspnea, and anorexia is severe. There may be slight fever, but in many cases the temperature is never elevated. Dull, aching pain in the chest is a common complaint. The first visible roentgenographic change often is not noted until the symptoms have been present for a week or more. The first change in the chest film is a diffuse haziness, most marked in the hilar areas. This represents an interstitial pneumonitis which is present before accumulation of intra-alveolar exudate, and it does not greatly increase the density of the roentgenogram. Gradually, over a period of some days, irregular opaque areas develop. These are more marked in the lower lobes but often extend throughout nearly all the parenchymal tissue. The history of exposure to beryllium and the clinical picture of the disease must be known by the radiologist if he is to make the diagnosis.

The pathologic changes in acute beryllium pneumonitis consist of (1) thickening of the alveolar walls by exudate, (2) edema fluid and small, round cells, and (3) filling of the alveolar spaces with exudate of lymphocytes, large phagocytes, and debris. Even in early cases one often observes the presence of early granulomas and of a tendency toward fibrous organization of the exudate.

The course of the acute disease is protracted, usually lasting at least three weeks and often as long as three months. About 10 to 20 per cent of the patients die. The only treatment is supportive; large amounts of oxygen are required throughout the critical period of the disease.

The chronic disease may start insidiously while the patient is still working, or he may have left his job some months or even years previously. He may have been exposed while employed in an industry where the danger of exposure to beryllium is unknown—and this is being recognized in all parts of the country and occasional cases are being reported. Often these cases involve maintenance employees who remove worn-out fluorescent tubes and break them or even burn them. The latter is an extremely dangerous procedure, because it releases hot fumes of beryllium. There also have been cases in which persons employed as benders of neon tubes did not know that the tubes were lined with toxic material. Other cases have occurred in men employed in the manufacture of certain alloys of copper, and in still others the source of exposure has not been determined. In one community, a number of nonoccupational cases occurred among persons exposed to exhaust fumes and dusts from a plant that extracted beryllium from its ore. A few women have become ill after inhaling the dust brought home on the clothing of their husbands who worked in plants where compounds of beryllium were used.

The first symptoms are usually shortness of breath, dry cough and loss of weight. The



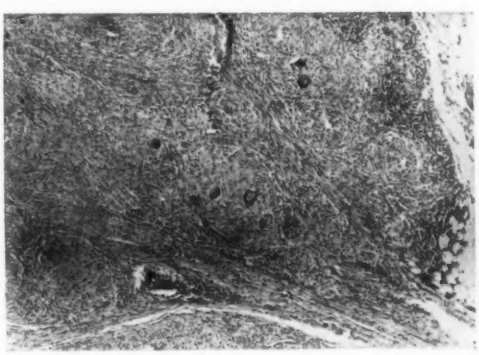


FIGURE 1. Chronic pulmonary berylliosis. Chest film of patient who worked in and resided near a beryllium reduction plant before entering the armed forces. After several years, he was discharged from the army, and his final service film revealed miliary densities of the lung fields. He subsequently developed dyspnea and cough, and analyses of urine revealed beryllium in occasional samples. *(Top.)*

FIGURE 2. Beryllium granuloma of skin. Photomicrograph of cross section through edge of ulcerated area of hypothenar eminence of boy who had sustained a laceration from a broken fluorescent tube three months previously. The granulomatous nature of the reaction is apparent (x 160). *(Center.)*

FIGURE 3. Beryllium granuloma of skin. Photomicrograph of tissue from depth of lesion shown in Figure 2, illustrating the tubercle-like beryllium granulomas (x 160). *(Bottom.)*

roentgenologic picture almost always shows some changes even in the early cases. There is a fine, diffuse nodularity scattered over the entire chest film, and this nodularity is superimposed on a slightly increased density of the lung fields (Figure 1). Roentgenograms in moderately advanced cases show conglomeration and "hardening" of the shadows, and the nodules are more definite out in the peripheral portions of the chest film.

As the disease progresses, the film becomes more dense, but always there is a "stippled" appearance to the lung fields. Emphysema becomes pronounced, the pleural surfaces become fibrotic, and at autopsy it is difficult to lift the lungs out of the thoracic cavity because of pleural adhesions. The lungs do not collapse, are firm and heavy, and many nodules 1 or 2 mm. in diameter are visible on the cut surfaces. The microscopic picture shows emphysema and nodularity throughout the tissues. The granulomas are scattered throughout the tissue, but they tend to have a juxtavascular distribution, and it is thought that this is one of the factors that contributes to a serious complication that occurs in this disease, namely, cor pulmonale. Nearly all the patients who have died of chronic pulmonary berylliosis have had cor pulmonale.

The course is prolonged. Patients soon become so dyspneic that they cannot walk up even one flight of stairs; then they become bedridden and develop clubbing of the fingers and chronic cyanosis. The illness tends to be progressive, and the great majority of patients die from one to four or five years after the onset of symptoms.

In some cases, however, there has been a spontaneous remission, not complete, perhaps, but enabling the patient to resume normal or more or less active participation in business. There also appears to be a likelihood that ACTH or cortisone may be of considerable benefit in relieving some patients of disabling symptoms.

SKIN LESIONS CAUSED BY BERYLLIUM

The beryllium ulcer is a lesion that develops after soluble beryllium compounds have become imbedded in the skin. It affects persons employed in beryllium-ore reduction plants, is extremely painful, and often requires excision.

The contact dermatitis and the conjunctivitis appear to be sensitivity manifestations, since they occur only in a certain proportion of the persons exposed to the offending agent, but they point up an interesting fact relating to the entire subject of diseases caused by beryllium, namely, that among the persons exposed only a relatively small proportion acquire the disease. There seems to be an important individual factor involved, whose nature is not yet understood.

A number of cases of cutaneous granuloma have followed the breaking of fluorescent tubes and the accidental laceration of the skin by fragments of glass that have the powder adherent to them. In one such case, a boy was playing baseball near a rubbish heap. He picked up a discarded fluorescent tube and hit the ball with it. The tube shattered and the boy's face was pelted with particles from the broken tube. Three months later there was an elevated, red scarred area, with focal ulcerating and fungating lesions, and extensive surgery was required.

In another case, a small boy broke one of the tubes in his hand. An extensive ulcer developed on the hypothenar eminence and complete excision was necessary. In both these cases, as in all others like them, the basic lesion was a granuloma that simulates the miliary tubercle, but which can be differentiated from it by the history of the injury, the absence of tubercle bacilli and the presence of beryllium as proved by spectrographic analysis (Figures 2 and 3).

AIDS TO DIAGNOSIS

If a patient's history suggests that he unknowingly might have been exposed to beryllium, there is one way that may help to determine whether or not this was the case, namely, to have his urine analyzed for the presence of beryllium. It has been shown that persons who have been exposed to beryllium will nearly always excrete beryllium in the urine for some time afterward. The presence of beryllium in the urine does not mean that any disease present is due to beryllium, but if the patient's history suggests that he might have berylliosis, if the chest film is consistent with this diagnosis, and if the urine contains beryllium, it is very likely that the disease is berylliosis. Another helpful procedure in diagnosis is pulmonary biopsy with microscopic and spectrographic analysis of the sample.

RETROLENTAL FIBROPLASIA

The Schneider Foundation Eye Presentation

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Retrolental fibroplasia
affects the eyes of premature infants
of low birth weight.
Its etiology is undetermined and no treatment has so far been
markedly effective. Vitamin E
has been used prophylactically but
results are still inconclusive.
Studies on use of ACTH are reviewed
but sufficient data are
not available to determine
its place in treatment
of this disease.

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It is indeed an honor to be asked to follow an illustrious group of ophthalmologists in presenting the annual lecture bearing the name of a great physician in our branch of medicine. His wide interests included the problems of the blind and their social and economic implications. Such a problem is the one which I am to discuss. It has been estimated that with the present rate of survival of premature infants in this country there may be as many as 650 children a year who are blind as a result of retrolental fibroplasia. Even with a considerable reduction in this figure, if it be too high, we will still have a serious situation.

DEFINITION

"Retrolental fibroplasia" is the name given by Terry to a condition in which a membranous growth develops behind the lens in the eyes of prematurely born infants who have low birth weights. The disease is not apparent at the time of birth but becomes evident after four to six months have passed. In the fully developed case, there is a grey, white or slightly yellowish membrane, sometimes showing blood vessels, seen back of the crystalline lens. There may be hemorrhagic areas in the membrane. When viewed in the extreme periphery, usually, finger-like, dentate processes can be seen.

HISTORICAL

Terry's preliminary report of this condition was made in 1942. In the 10 year period since that time many other reports have been made. Previously, sporadic cases of similar nature were reported in the literature under a variety of names and with no special uniformity in either the age or weight factor, i.e., the connection with prematurity. In the past 10 or 12 years, however, there has been a marked increase in the incidence of the disease, seemingly coinciding with the numbers of premature infants that are saved, and especially those of the lower birth weights. Kinsey and Zacharias point to the fact that the survival rate at the Boston Lying-In Hospital has not increased significantly in the past 16 years and quote a Children's Bureau report of 1948 which suggests to them that any increased survival rate in prematures is small compared to the apparent increase in incidence of retrolental fibroplasia. It has been thought by some that perhaps the difference lay in the fact that more of the smaller infants are surviving.

Terry, who described the disease in its fully developed stages, at first considered that the membrane arose from the fetal vascular system of the lens, the tunica vasculosa lentis, which persisted in eyes which were not fully developed, with replacement by fibrous tissue. Reese and Payne thought that it all arose from persistence of the primary vitreous with subsequent hyperplasia. Krause originally felt that it was a general dysplasia involving the cerebrum as well as the retina. Owens and Owens showed that there was an associated retinal angiomatosis and considered that this was essentially the basis of the condition. In this connection, Reese has called attention to the relatively large number of these cases in which there are angiomatous lesions elsewhere. He has been supported in this observation by Klien and Owens and Owens.

In later papers, Reese and Blodi divided congenital or early "leukokoria" or "white pupil" into three main groups:

"1. Retrolental fibroplasia occurs primarily in premature infants and is the lesion which has shown the tremendous increase during the past decade or more.

"2. Persistent hyperplastic primary vitreous occurs in full-term infants, is unilateral, and includes the cases referred to as 'remains of the tunica vasculosa lentis.' Its incidence has not increased.

"3. Retinal dysplasia is a bilateral congenital malformation manifesting itself at birth in full term infants in association with cerebral agenesis and congenital abnormalities elsewhere over the body."

DIFFERENTIAL DIAGNOSIS

The conditions described by Reese and Blodi must not be confused with congenital cataracts, "glioma" of the retina occurring in an infant, metastatic retinitis, so-called pseudoglioma, or massive retinal fibrosis. I have seen, in consultation, several cases of retrolental fibroplasia which had been thought to be congenital cataracts and for which surgery was contemplated. Some eyes have been removed because the growth was considered to be malignant. This has provided some eyes for study of the fully developed membrane, but barring complications, it is an unnecessary procedure.

INCIDENCE

The disease seems to be confined to America and is scarcely known abroad. There has seemed to be a great variation in its incidence in different parts of the country and in different cities. To the present time, most reports have come from Boston (where Terry first called attention to the condition), New York and Baltimore—with lesser numbers from Cincinnati, Chicago, Hartford, Denver, etc. The larger numbers in certain centers are probably more apparent than real. The geographic distribution is much wider than would appear, since children are brought from distances when it is known that a special interest has been shown by an institution or an individual. For example, the children I have seen are not all from Minneapolis, but from the entire state of Minnesota as well as part of Wisconsin and from as far west as Montana. According to the figures of Owens and Owens and those of Kinsey and Zacharias, the average incidence of retrolental fibroplasia is about 8 per cent in babies whose birth weight is between 3 and 4 pounds,

and 16 per cent in those under 3 pounds. It seldom develops in those whose birth weight is between 4 and 5½ pounds, and extremely rarely in full term babies. Our own figures, which have not as yet been published, parallel this very closely.

DEVELOPMENT OF CLINICAL PICTURE

The best opportunity for study of the development of retrolental fibroplasia has been at Johns Hopkins Hospital where, in 1945, a special premature center was established and arrangements were made for any premature infants born in the state of Maryland to be transported quickly to this nursery. I quote directly from Owens and Owens their description of the typical development of retrolental fibroplasia, as seen clinically:

> At birth the eyes of the infants who subsequently develop retrolental fibroplasia are entirely normal and indistinguishable from those of the other premature infants who do not develop the disease. The earliest detectable abnormality of retrolental fibroplasia is a dilation of the retinal arteries and veins. This usually occurs about three to five weeks after birth. As the vessels increase in size they become very tortuous. Often the arteries become so tortuous that they turn backward on themselves in hairpin curves. In some cases the arteries become so tortuous they resemble the ribbon candy usually seen at Christmas time.
>
> These vascular changes are followed by the appearance of generalized or localized grayish-yellow areas in the retina. When first seen these grayish-yellow areas are solid and elevated. Occasionally numerous small hemorrhages occur on the surface of the retina or in front of it. If the retinal changes are generalized the entire fundus becomes grayish-green in color. After some days the vessels become obscured, the margins of the disk blurred, and a generalized vitreous and retinal haze finally develop.
>
> If the disease progresses the retina becomes detached and appears as a gray mass with numerous vessels coursing over it, billowing forward in folds at the periphery of the space behind the crystalline lens. This retrolental mass is the anterior portion of the swollen retina. At this stage the fundus can be only hazily seen and the retina has been greatly disorganized. Bands of tissue containing vessels grow out from the areas of detached retina into the vitreous. Finally a complete membrane is formed behind the lens by the gradual extension and fusion of the disorganized, detached retina. Occasionally small hemorrhages occur into the retrolental fibrous membrane. At this stage of the disease the eye stops growing, and remains small. The disease not only destroys the retina but prevents further growth of the globe. Later some of the eyes show secondary changes, such as glaucoma and iritis.
>
> Occasionally the disease becomes arrested at the stage in which only a partial membrane has formed behind the lens, and in some of these eyes partial imperfect vision may be maintained.

PATHOLOGY

Pathologically, there has been adequate opportunity to study many sections of eyes showing retrolental fibroplasia in stages of development corresponding to the clinical picture seen in infants who for one reason or another did not survive. Recently Friedenwald, with the Owens', has shown the very earliest changes and definitely placed the first beginnings in the retina in the region of the ora serrata. These changes consist in budding proliferation of the capillaries, forming glomerulus-like loops, and continuing proliferation of the endothelium with irregular patches of proliferating glial cells. This is followed by edema and small hemorrhages until there is a breakthrough into the vitreous, with further proliferation and separation of the retina. Parker Heath, who last year gave an exhaustive paper on the pathogenesis and classification of retrolental fibroplasia, has recently published further studies on the pathologic changes shown in the development of the disease, with similar changes in the oral region: (1) endothelial proliferation, hemorrhage and edema, in an incompletely differentiated retina, with marked congestion of the uvea; (2) extension of the protein-rich edema, neovascular tissue and hemorrhage into the vitreous, with an angio-fibrous organization of the vitreous, followed by retinal separation and retrolental membrane; (3) pathologic repair and atrophy.

ETIOLOGY

It is understandable that there has been and continues to be much thought and work put into the study of the etiology of this grave condition. In order to begin any serious considera-

tion of a specific cause it is necessary to determine if the probable origin is pre- or postnatal. If prenatal, what is the influence of intercurrent infections or other abnormal conditions in the mother; of prenatal medication and the conditions of delivery, etc.? If studies show no influence that seems common to all, efforts should be concentrated on postnatal influences.

In their study of the incidence of retrolental fibroplasia, Kinsey and Zacharias found that there was no significant influence exerted by the parity or age of the mother, the Rh type, the type of delivery, the analgesics or anesthetics used, the causes of premature delivery, single or multiple births, sex, and congenital anomalies. At Columbia, the same conclusions were reached in a study of 104 pregnancies which resulted in retrolental fibroplasia in the offspring. Other studies, while not so extensive, seem to confirm these findings. Harold Falls, in a discussion of one of Reese's papers, stated that no evidence of a hereditary factor had been found. Almost never has there been more than one child in a family affected, though we have seen two survivors of triplets, both girls, with fully developed retrolental fibroplasia, the nonsurvivor being a boy.

It is quite generally agreed that no prenatal influence is responsible etiologically, so attention has been directed toward possible postnatal factors. As a postnatal possibility, a virus has been considered and some work has been done in trying to determine its presence. There has been no proof that such a virus is present. Another suggestion was made by Krause that the effect of light on the eye tissues, which were as yet unprepared for it, might be to blame. He himself has answered this question by finding that, when kept completely away from light, some premature infants develop the disease.

In some of his later writings, Terry changed his view that the lesion was present at birth and suggested that the development occurred in infants who, among other things, were not physiologically prepared to digest and assimilate their food; i.e., that the condition resulted from a form of malnutrition and avitaminosis. Kinsey and Zacharias also concluded that the methods of feeding in various institutions, particularly the administration of vitamins and iron, bore a relationship to the development of retrolental fibroplasia. Owens and Owens called attention to the fact that for many reasons having to do with metabolism, there is a serious vitamin E deficiency in the premature infant; the smaller the child, the more severe the condition.

TREATMENT

With the idea of vitamin E deficiency in mind, Owens supplemented the feedings of a group of prematures, weighing less than 3 pounds, with vitamin E as synthetic dl-alpha-tocopherol acetate. This procedure was begun as soon as the infant was able to take feedings. Another group, from whom the supplementary vitamin was withheld, was used as control. After finding no retrolental fibroplasia in the first group of 11 infants and 5 cases in the 15 infants in the control group, all infants whose birth weight was under 3 pounds were given this supplement. Of the total of 101 cases reported, 23 received vitamin E, of whom 4.4 per cent developed retrolental fibroplasia, while of 78 who did not receive this supplement, 21.8 per cent were so affected. The authors commented that "it seems certain that the solution to the etiology of retrolental fibroplasia will be found from such a metabolic study." With further study they have concluded that the use of the vitamin did not reduce the incidence of early ocular changes, but that there was a distinct effect on the number of infants who developed complete retrolental membranes.

Reese and Blodi reported no difference in two groups, one of which was given vitamin E, and the other not. Kinsey and Chisholm have recently reported that, in their studies on the administration of vitamins, there was no reduction in the severe form of the disease in those who showed early vascular changes. Even in those infants who, from birth, were given vitamin E prophylactically, development of various grades of vitreous and retinal pathology occurred—5 per cent to the stage of retrolental membrane formation. These authors believe, in spite of these findings, that further use of this medium should be made so that additional data may be accumulated for its evaluation.

With the advent of ACTH and cortisone, it was natural that they should be tried in the treatment of retrolental fibroplasia. Too few reports are at hand to evaluate the results obtained. ACTH has been used in therapeutic trials, but conflicting reports leave open the question of its efficacy. Reese is one of the investigators who has felt that, because of the nature of the disease in its early phases, ACTH would be useful. To that end, he treated 14 cases which were apparently advancing toward fully developed retrolental fibroplasia with 25 to 50 mg. daily, enough to inhibit bone growth. In all of the cases, the progress of the disease stopped, while progression continued in 3 of 5 untreated cases in the group. Scheie and his co-workers found encouragement in 1 case out of 5 treated and felt further trial was advisable. Other reports have been discouraging.

Thus, it is seen that, at the present time, there is no established treatment. Naturally, parents of these unfortunate youngsters are anxious to have something done and the question of surgery usually arises. From the very nature of the condition, surgery is obviously of no avail in restoring function to a blind eye whose retina has become an integral part of a fibrotic mass. In children who develop glaucoma, it is sometimes necessary to do a filtering operation, especially in those cases in which there is some slight visual function remaining. In most cases, however, it is better to enucleate an eye which is blind and when it is clear that pain and discomfort are present.

SUMMARY

1. Retrolental fibroplasia is a disease affecting the eyes of premature children of low birth weight, usually under 4 pounds, with progressive increase in incidence as the weight decreases.

2. The rapid increase of this blinding disease is serious when considered from the social, economic and educational standpoint and it constitutes a grave problem for physician and public health worker.

3. The etiology is undetermined. Prenatal influences are generally believed to have no bearing on the causation. No postnatal influence has yet been established as the definite cause, though studies show that there is some evidence of disturbed metabolism, per se, and that present hospital management of treatment may have to be altered.

4. No treatment has to the present moment been effective to any marked degree. The use of vitamin E, prophylactically, as a supplement to the feedings gave some promise of effectiveness, when begun before any signs were visible ophthalmoscopically. ACTH has not been used long enough to determine its place, though a few cases apparently respond if early use is instituted. When fully developed there is obviously no treatment.

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CLINICAL ASPECTS OF Q FEVER

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Q fever is distributed widely over the world. The disease was originally classified as a rickettsial disease, but certain differences in the organism, mode of transmission, and clinical aspects separate it from this group. Clinically the disease resembles an acute infection with many cases developing atypical pneumonia. Streptomycin, chloramphenicol and aureomycin are of value in treatment.

Q FEVER was first recognized in Australia by Derrick in 1937. The next report of a naturally acquired infection was made by Hesdorffer and Duffalo in Montana in 1941. Since that time, the disease has been found in many areas throughout the world—Greece, where it was first called Balkan grippe, Bulgaria, Romania, Italy, Panama, Switzerland, Great Britain, Turkey, Portugal, Algeria, Israel, South Africa, Mexico, Germany, France, Spain and Yugoslavia. In the United States, Q fever has been recognized in Montana, Texas, Illinois, Arizona, California, Pennsylvania, Massachusetts, New York and Washington.

In addition to cases occurring in the general population, many infections have occurred among persons working in laboratories where the causative agent of Q fever has been under investigation. Among laboratory personnel, Q fever has a record of infectivity comparable to the records established by such infections as brucellosis, tularemia, typhus and psittacosis. The first laboratory infection was reported in connection with the original Australian outbreak. Since that time, many laboratory infections have occurred in practically every laboratory throughout the world where studies of Q fever have been undertaken.

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ETIOLOGY

The causative agent of Q fever was first classified as a Rickettsia, and was named *Rickettsia burneti*, the disease itself being regarded as belonging to the rickettsial group of diseases. However, because of certain differences in the viability of the organism, the mode of transmission and clinical aspects, the causative or-

ganism has been renamed *Coxiella burneti,* and the disease itself is regarded as being closely related to, but somewhat distinct from, the true rickettsial diseases. The differences between *C. burneti* and the true rickettsiae rest in the filterability of *C. burneti* and its greater resistance to physical and chemical agents.

R. E. DYER

TRANSMISSION

In the modes of transmission, the rickettsial diseases depend on an arthropod host for survival and are transmitted from animal to man or from man to man by specific arthropods. In regard to Q fever, it is true that seven species of ticks have been found naturally infected with *C. burneti,* and five additional species have been experimentally infected. Coxiellae also have been isolated from wild animals, and it would appear that the tick may play a part in keeping the infection alive in nature, but the importance of this role remains unknown at present. Instances of human infection have been recorded in which the infection probably resulted from exposure to ticks in nature, but these arthropods apparently are of little importance in direct transmission of the disease to man.

The great majority of the cases which have been reported have occurred among persons exposed to domestic livestock, cattle, sheep and goats, or their products. Examples of these are slaughterhouse employees, dairy workers, and those living in the neighborhood of dairies or consuming raw milk from infected cows. In one outbreak, association with pigeons, rats and mice was noted. Outbreaks also have been reported among workers in plants engaged in the processing of wools and hides. In one instance, cases of Q fever occurred among the employees of a laundry servicing a laboratory where active research work on this disease was in progress. Report has been made of the occurrence of 19 cases among 75 employees working in an establishment where a printing press was uncrated. The cases were believed to be caused by the dust from the straw in which the press was packed. It is interesting to note that this outbreak occurred in Switzerland and that the printing press had been shipped from Ohio.

The actual mode of transmission from animals to man has not been learned. Since the organisms withstand drying and remain viable for long periods at ordinary temperatures, the inhalation of dust particles contaminated with material from infected animals would seem to be important.

In the California area, *C. burneti* have repeatedly been isolated from the raw milk of dairy cows and, on autopsy, from the mammary gland and the adjacent lymph nodes. The infected cows shed the organisms for long periods of time. In affected areas, extensive laboratory examinations have shown that material contaminated with raw, infected milk, or placental membranes from parturient cows is a fruitful source of infection. In a study recently reported from the same area, the air samples taken over areas occupied by cattle or sheep known to be infected with Q fever were found to contain *C. burneti.* In one instance, the samples were taken from a pen where 36 cows from an infected herd had been kept. In a second isolation, the air samples were taken in a barn where sheep infected with Q fever had been housed 30 days previously. Air samples taken over a yard where the same flock of sheep was subsequently herded were also found to carry *C. burneti.* Among persons coming in direct contact with livestock, as in slaughterhouses, inhalation of droplets of infected material would seem to be a possible mode of infection.

In general, secondary infections have not occurred from contact with patients ill with Q fever under conditions where other sources of infection could be ruled out. Recently, reference has been made to the probable transmission of Balkan grippe (Q fever) from man to man by infected droplets of sputum. In another instance, 3 cases of Q fever occurred among hospital employees who had attended a patient sick with the disease. Report also has been made of 38 cases of Q fever in a hospital ward where a laboratory assistant with Q fever was under treatment. Coxiellae were found in the sputum

of this patient, and no other source of infection could be established.

CLINICAL FEATURES

The clinical difference between Q fever and the true rickettsial infections lies in the general absence of a rash in cases of Q fever. Exceptions to this will be noted later.

The clinical descriptions of Q fever from data gathered from widely separated areas in general give the same picture as that presented in Derrick's original report, with the important addition of the discovery of lung involvement closely resembling that seen in cases of primary atypical pneumonia. This complication was first noted in a laboratory outbreak, and has later been found of common occurrence in naturally acquired infections.

INCUBATION PERIOD

The incubation period of Q fever varies from 12 to 30 days with a common length of 14 to 18 days. Prodromal symptoms are not often seen although occasional patients complain of weariness, lassitude and headaches 12 to 24 hours before the onset of fever. In other cases, the individual may remain at work for two or three days after the actual onset. In one laboratory outbreak, 4 of the patients reported mild, temporary illnesses about one week before the beginning of the attack of Q fever.

SYMPTOMS

In the majority of cases, the onset is sudden, many patients being able to state the exact time they became ill. Headache, malaise, chilliness or frank chills are the most common of the early symptoms which coincide with the beginning of fever. During the illness, insomnia may also be present. The headache is most often frontal and is often accompanied by pain in the neck, photophobia, retro-orbital pain and soreness of the eye muscles on movement of the eyes. Burning of the eyes, lacrimation and conjunctival congestion have been seen in some of the cases. Stiffness of the neck, aching of the lower extremities, soreness of the joints, and sense of fullness behind the sternum are not uncommon. Cough is present in practically all patients having pneumonitis. Bloody sputum is not often encountered. If the cough is productive, the sputum is small in amount and is a thick, tenacious, white mucus. Chest pains are not uncommon and are apt to be substernal with increased pain on coughing. Nausea, vomiting, diarrhea or constipation may be present. Anorexia is almost always present at the onset and during the acute stage of the illness. This may be followed by a loss in weight in severe illnesses, in some instances being as great as 25 pounds. Among older people with severe attacks, some degree of disorientation and confusion may be present. In one severe attack, wild delirium was reported.

TEMPERATURE

Fever is usually remittent, with occasional patients showing intermissions. In the course of 24 hours, the temperature may vary from 100° F. to 104° F., and occasionally higher. Usually the fluctuation is less pronounced if salicylates are not used in treatment, although marked fluctuations have been reported in some patients not receiving antipyretics. The fever may be present for periods ranging from a few days to three weeks and occasionally as long as three months, the usual duration being 6 to 10 days, usually disappearing by lysis over a period of several days, although defervescence may take place more rapidly in some cases. Chills varying in intensity from chilly sensations to frank rigors are present in practically all cases, and are often followed by profuse sweats. Sweating may also occur following drops in temperature without preceding chills. In some cases, chills appear with the onset of the acute illness, while it is not unusual for them to develop about the third or fourth day of the illness, reappearing at intervals until defervescence.

PULSE

The pulse rate is low in comparison with the temperature in practically all cases. The rate tends to rise with the temperature, with an increase of about seven beats per minute with

each degree rise in temperature, seldom exceeding 100 beats per minute.

RASH

As stated earlier, the absence of a rash is one of the characteristics which has placed this disease a little apart from the true rickettsial diseases. With a few exceptions, the clinical reports of Q fever do not mention a rash. However, in a few reported cases temporary rashes of a maculopapular character have been described, appearing first on the back and later on the chest and abdomen. In one outbreak in a mental hospital, 60 cases occurred. It is reported that about half of these patients developed rashes consisting of large scarlatiniform macules on the entire trunk or on the dorsal lumbar regions. The rashes on these patients lasted from one to three days. In general, however, it may be stated that persistent rash, aside from one caused by medication, would not be consistent with the common clinical picture of Q fever.

LUNG INVOLVEMENT

On physical examination of the chest, abnormal physical findings are often negative for the first few days, with the later development of slight rales and mild dullness, usually over the lower part of the chest, in many cases. Chest pains when present are usually minimal in character. There is usually no significant rise in respiration rate, and no dyspnea. A majority of the patients develop lesions which are sometimes found only on roentgenologic examination. Roentgenographic findings resemble very closely those seen in cases of primary atypical pneumonia. A soft, infiltrative lesion is visible on the film. This lesion is not of the uniform density seen in lobar pneumonia. The areas of consolidation are patchy in character with a ground-glass appearance, and usually only a portion of a lobe is involved. Shift of the interlobar septum with some collapse of lung tissue is often noted. In the majority of cases only single lesions occur, although some cases have shown involvement in more than one lobe. Usually the lower lobes are involved. Roentgenograms made during the first two days often fail to show consolidation, since this usually appears on the third or fourth day, and occasionally later. In many cases, roentgenographic studies have shown the persistence of lesions for two or even three weeks, sometimes accompanied by return of fever and symptoms of the acute illness.

COMPLICATIONS

Among the complications that have been noted following severe cases are arthritis, epididymitis, esophagitis, intestinal hemorrhage and decubitus ulcers. One case of encephalitis has been reported as a complication. The encephalitis developed eight days after defervescence. The patient developed tremor of the right hand, with diminished sensitiveness to touch over the hand and arm, diplopia, slurring of speech, lassitude, inversion of the sleep period and exaggerated knee jerks. Recovery was complete after a period of six weeks. Convalescence is usually fairly rapid, with most patients complaining of moderate weakness for two or three weeks after cessation of the fever.

In the reports of early investigations in Australia, a case is recorded which showed a daily rise in temperature for nine weeks after the onset of the acute illness, while a second case showed relapses over a period of nine months after the initial illness. These relapses were characterized by the signs and symptoms and laboratory findings commonly seen in the primary attack. In a small percentage of severe cases, sequelae develop such as intermittent attacks of fever, swelling of the ankles and pain in the back or legs. These sequelae may be present for several weeks or months after the acute illness has subsided.

Mild, moderately severe and severe cases may occur in the same outbreak, the attacks being apt to be more severe in patients in the older age groups.

The mortality rate is low for Q fever occurring in human beings, being less than 1 per cent in cases recorded at present.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis, psittacosis, coc-

cidioidomycosis, influenza and primary atypical pneumonia present clinical pictures which closely resemble Q fever. Brucellosis and typhoid fever have to some extent confused the diagnosis in some instances. In an early outbreak in a meat-processing plant, in an area where Q fever was not known to be present, 33 patients with Q fever were treated by 32 physicians, only 1 physician having seen 2 of the patients. No diagnosis was made in 12 of the cases. In the remainder, the various diagnoses were: lobar pneumonia (7 cases), influenza (4 cases), grippe (2 cases), gastritis (2 cases), and pharyngitis, atypical pneumonia, bronchitis, upper respiratory infection, brucellosis and tuberculosis (1 each). In another outbreak of over 200 cases, 70 per cent were diagnosed as atypical pneumonia while subsequent tests indicated that the outbreak was in reality Q fever.

In experimental work with guinea pigs, solid immunity is found to exist and, as far as is known, immunity produced by an attack of Q fever in man is persistent.

LABORATORY FINDINGS

Routine laboratory examinations show little of importance in assisting in the diagnosis. Albuminuria is commonly present during the acute febrile stage. The blood count usually remains within normal limits with occasional cases showing slight increases; the sedimentation rate commonly is elevated during the acute period of illness and returns to normal in early convalescence. All common agglutination tests including the agglutination of *Proteus X19* are negative. Laboratory confirmation of the diagnosis of Q fever can be made in three ways: (1) by recovery of the organisms by animal inoculation (the guinea pig being the animal of usual choice, mice also being susceptible); (2) by the complement fixation test, or (3) by agglutination of suspensions of the organisms by the patient's blood serum.

Isolation in guinea pigs of the agent from the blood of the patient is usually successful. After the strain is established in guinea pigs, a spleen emulsion from the infected animals may be used to inoculate the yolk sac of the developing chick embryo, or the inoculation may be made using defibrinated blood and serum from the patient. Mice also may be used for the initial isolation. In the guinea pig, the incubation period varies from 5 to 14 days. After the incubation period, these animals develop temperatures ranging from 40° C. to 41° C. This temperature usually lasts from one day to one week. The death rate varies with the strain. Guinea pigs infected with some strains show high fatality rates, while animals injected with other strains show a very low fatality rate. The most characteristic gross finding on autopsy of the guinea pig is an enlarged spleen, sometimes being three to five times the normal size. The identification of Q fever in the animal is made by serologic tests or by the development of immunity against a challenge dose of a proved strain of *C. burneti*.

The complement fixation test is the method of choice for laboratory diagnosis. Either the technic described by Bengston or a modification of the Kolmer technic may be used. In human cases, significant complement fixation titers usually appear during the second week of the illness, the highest titers often being reached in the fourth or fifth week. The titers usually run from 1:160 to 1:2,560. High titers are maintained for a few weeks after recovery and may persist for 18 months or more.

Development of specific agglutinins in the patient's blood serum occurs usually during the second week after onset of the acute illness.

AUTOPSY FINDINGS

In the few human cases that have come to autopsy, a state of red and grey consolidation has been noted in the lung. The exudate of the consolidated areas is predominantly of the mononuclear cell type, most of the cells being swollen and degenerated macrophages in which coccoid and bacillary forms of Coxiellae have been demonstrated. These organisms may be both intracellular and extracellular. The Coxiellae have also been found in macrophages of the spleen and the testes, and in brain cells.

TREATMENT

The general treatment of Q fever is symptomatic. Salicylates are often used to give relief.

In some cases, sedatives are necessary for the control of insomnia and headaches. Penicillin and the sulfonamides have been used without success. Some patients apparently have shown some response to streptomycin and chloramphenicol. At present, aureomycin seems to have some value in the treatment of this disease, this value having been first indicated in animals and later by clinical trials. In experiments with animals, it has been found that aureomycin has marked therapeutic activity against Q fever. Animals with Q fever become afebrile in 48 to 72 hours after a subcutaneous dose of 5 to 6 mg. per kilogram of body weight.

In a series of cases occurring in California during one year, 45 patients were treated with aureomycin. Oral, intravenous and intramuscular administrations were used. In oral treatment the amount given varied from 1 to 5 gm. during each 24 hours, the drug being given in equal doses at four to eight hour periods. The intravenous dose was 200 to 300 mg. in 24 hours, and the intramuscular dose ranged from 40 to 400 mg. in a like period. The intramuscular injections caused severe pain and inflammation at the injection site. A majority of those treated by the oral route developed nausea. Aside from this there was little evidence of toxicity. A majority of the patients treated became afebrile within five days after treatment was begun; others showed some improvement, while in a small number there was little or no evidence of benefit. The authors of this report conclude that aureomycin is useful in the treatment of Q fever, but that it is not invariably effective.

IMMUNIZATION

Work has been done in the preparation of vaccines, and experiments on the lower animals and human volunteers indicate their value. The vaccine is prepared from Coxiellae grown in the yolk sac of the developing chick embryo, after the method used in the manufacture of the vaccines against typhus and Rocky Mountain spotted fever. In one test using guinea pigs, the animals later showed definite resistance to the challenge doses. Human volunteers given the same vaccine used in the animal test showed specific complement-fixing antibodies in titers of 1:20 or over, two weeks after vaccination. No data from field tests are available to indicate the practical value of such vaccines. So far, no case of Q fever has been reported as occurring among laboratory workers who have been vaccinated.

SUMMARY

In Q fever we have a disease apparently of world-wide distribution. Ticks may play a part in the maintenance of this infection in nature by transmission from animal to animal, but with the exception of a few instances these arthropods are not of importance in causing human infections. The great majority of cases occur among persons exposed to infected animals or their products—particularly raw milk—whether by occupation or place of residence. The disease is highly infectious in laboratories where the causative organism is under study. The clinical features are those of an acute infection, with a majority of the cases showing lung involvement. Definite diagnosis can be established by serologic methods or by isolation of the causative agent. Aureomycin appears to have some value in treatment.

An extensive bibliography on Q fever is available on request to the Editorial Department of *Postgraduate Medicine*.

DIAGNOSIS AND TREATMENT OF GASTRIC DIVERTICULA

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If judged merely on the basis of statistics, the subject of this diagnostic clinic might not appear too significant. However, I feel that one of the basic principles of good medical diagnosis is the consideration of all possible etiologic conditions which might result in a certain symptomatology. As I have told medical students time and again, in prognosticating the efficiency of a medical student as a physician 10, 15 or 20 years from now, I would not necessarily pick the one with the best grades, but I would pick the one who is thorough and suspicious and who at least considers the variety of conditions which might produce a given symptomatology.

The physician who makes a diagnosis after pathologic study of a microscopic section from a rectal lesion cannot consider the examination to be complete unless he also has done a digital examination. The same principle can be applied to many other conditions, such as tumors of the breast. Academic description of the microscopic findings in breast lesions are of no use unless the possibility of a lesion in the breast is considered and the lesion discovered.

Statistically, gastric diverticula are not too common. However, they are increasingly significant in that medical literature is beginning to contain more and more reports on this condition. One fundamental reason for this increasing significance is improved radiologic technic. Gastroenterologists are becoming interested in the nature of the abnormalities which exist in the superior portion of the stomach, in the vicinity of the esophagus. We now have surgical procedures for achalasia, cardiospasm, paraesophageal hernias of the stomach, and so on. This specific area is the most frequent site of gastric diverticula.

INCIDENCE

Available statistics show that in a series of over 4000 routine gastrointestinal examinations the incidence of gastric diverticulum was about 1 in 2000 or 3000. Eddy D. Palmer of Walter Reed Hospital recently reviewed the literature and recorded over 400 cases of true gastric diverticulum. Obviously there are many more unreported cases. In some of these, the radiologist or clinician may have felt that gastric diverticula, especially if they are asymptomatic, are not of sufficient interest to report; in others, the condition probably was not discovered.

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Gastric diverticula, though statistically uncommon, are being reported more frequently in medical literature. With the increasing interest in surgical lesions of the lower esophagus and upper stomach, the medical profession should keep in mind this condition as a problem of differential diagnosis. Two personal cases are discussed in the light of early recognition of gastric diverticula as a possible cause of vague upper abdominal symptomatology.

In 1936, L. Martin reviewed the Johns Hopkins archives and found not a single reported case of gastric diverticulum diagnosed preoperatively. In fact, only 4 cases had been recorded up to that time, and these reports were in the files of the pathology department.

Dr. Henry Pinkerton, professor of pathology at St. Louis University School of Medicine, tells me that during the past 10 years at the University Hospital, which has approximately 20,000 admissions a year, there has not been a single case of gastric diverticulum recorded in the files of either surgical specimens or postmortem examinations.

These statistics concerning the incidence of gastric diverticulum may indicate that the subject is of no significance. I want to emphasize, however, that one should not be lulled into a sense of security merely because statistics show that the condition is extremely rare. Within a period of one month, I encountered 2 cases of gastric diverticulum. Both patients were relieved by surgery, and I shall discuss them later.

Contrary to earlier reports that gastric diverticula are found primarily in women, their incidence has been found to be equal in men and women.

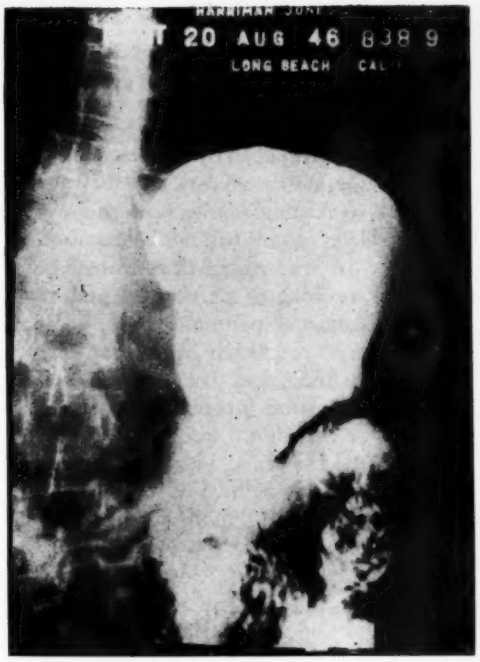

FIGURE 1 *(above)*. Roentgenogram taken in an oblique plane following barium meal, outlining gastric diverticulum in the usual location in the posterior aspect of the stomach.

FIGURE 2 *(below)*. Roentgenogram four hours after barium meal, showing retention in the diverticulum.

ETIOLOGY

There are two types of gastric diverticulum, namely, the false and the true. The false type,

as exemplified by an ulcer which erodes through the gastric mucosa and the muscularis, with a weakening in the wall and a subsequent ballooning-out, will not be discussed here.

A true gastric diverticulum exists as an outpouching of the stomach, and contains the fundamental portions of the stomach wall. It is lined completely by mucosa, except possibly for an ulceration that has developed, and the gastric pattern is continued in the wall of the gastric diverticulum throughout its entirety. Occasionally the serosa may be absent because of adhesions or because vessels which penetrate into the apex of the diverticulum may reflect the peritoneum.

The etiology of gastric diverticula has been divided academically into two main types, namely, the intrinsic and the extrinsic. Such academic partitionings remind me of my Latin days—all Gaul is divided into three parts, etc. The intrinsic factors are the basic mural deficiencies. There is another location where there is a mural deficiency similar to that in the region of the esophageal opening into the stomach, where the longitudinal gastric muscle is deficient or, at least, thins out, namely, where the pharynx joins the esophagus. This is another common site of diverticula.

Vascular penetrations into the wall of the stomach form natural pathways through which the extrinsic forces have their effect, such as pulsion from increased intraluminal tension. One can conceive a pouching-out of the stomach following the course of these vessels in their paths of penetration.

Pyloric obstruction is another cause, an extrinsic factor, resulting in an increased intraluminal tension and thereby possibly favoring a pushing-out through a weakness existent in the stomach wall, an intrinsic weakness.

SYMPTOMATOLOGY

There is no definite syndrome associated with gastric diverticulum. However, 50 per cent of the patients will complain of central substernal, lower thoracic or epigastric pain. This pain is not the typical pain of an ulcer. Patients do not have the vomiting and pain which are relieved by eating; in fact, eating may tend to increase the pain. If the stomach is empty and patients can tolerate the starvation factor, they are not too uncomfortable, so, I repeat, it is not a typical ulcer pain. It is a vague, epigastric, substernal type of pain.

Half the patients will complain of the type of pain just described, and approximately 30 per cent (total of 80 per cent) will have a vague dyspepsia. These are the patients in whom you look for a peptic ulcer, have a gallbladder series done, and request barium enemas, electrocardiograms, and so on, realizing that the complaints do not constitute a familiar clinical entity. Finally, the radiologist reports that he has discovered a gastric diverticulum. If you keep in mind that, besides paraesophageal hernia of the stomach, gastritis, achalasia of the esophagus, and so on, there is another condition which—though somewhat uncommon—can simulate these abnormalities, you will be able to diagnose these cases of gastric diverticulum.

COMPLICATIONS

Complications of gastric diverticulum are not as frequent as are those of diverticula occurring in other parts of the gastrointestinal tract. The acute type of diverticulitis is extremely rare. Chronic diverticulitis is more common, and I will elaborate on that in the discussion of the pathology.

Perforation is extremely rare, only 1 or 2 cases having been reported.

Despite the fact that some of these gastric diverticula show definite signs of ulceration, serious hemorrhage is relatively infrequent; this is even more surprising when it is considered that in many cases there are fair-sized vessels which penetrate the diverticulum through the apex.

Torsion is a very rare complication in cases of gastric diverticulum.

Carcinoma complicating a gastric diverticulum is a questionable point concerning which there is not sufficient evidence to make any definite statement; however, it is something that should be kept in mind.

I mention the following complication simply because of its rarity and interest: J. B. Hartley of England *(British Journal of Radiology)* report-

ed, of all things, a large gastric diverticulum residing in a left inguinal hernia.

LOCATION

About 75 per cent of all gastric diverticula are situated in a definite area within a 3 cm. radius of a point at the junction of the lesser curvature of the stomach and the esophageal orifice. They usually will be found just above the splenic artery and within 2 or 3 cm. of the lesser curvature of the stomach on the posterior surface. In other words, they are hidden unless the stomach is rotated or the lateral or oblique view is kept in mind when barium studies are done.

These diverticula are rarely multiple. They range in size from 1 cm. to 11 cm. in diameter, the average being 3 to 4 cm.

PATHOLOGY

The pathologic change involved in gastric diverticula—the factor that causes the symptoms—is retention. If it can be determined that these diverticula retain barium for periods longer than eight hours, you can be assured that food will be retained. The retained food will ferment, irritate and cause a chronic gastritis in this pocket lined by gastric mucosa, the gastric diverticulum. When this retention has been

FIGURE 3 *(below)*. Postoperative study of the stomach following barium meal, revealing absence of the diverticulum.

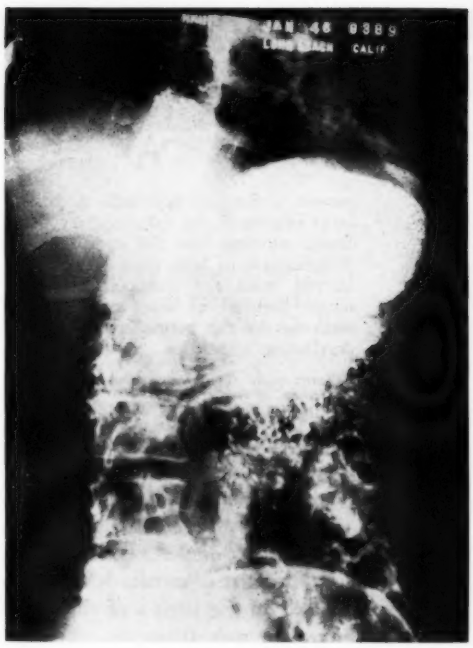

FIGURE 4 *(left)*. Surgical approach. The greater curvature of the stomach being more mobile, an approach through the gastrosplenic and gastrocolic ligaments with rotation of the stomach to the right proved more satisfactory than an approach by way of the lesser curvature and gastrohepatic ligament.

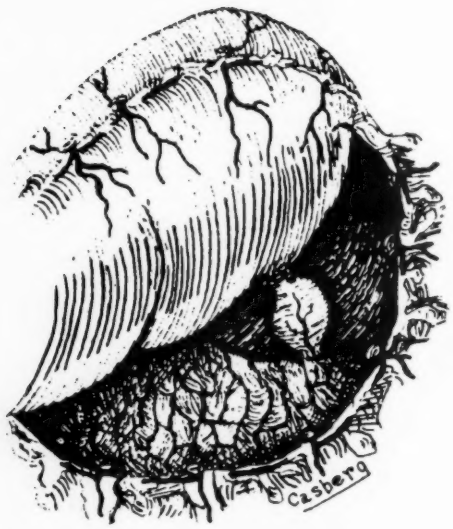

FIGURE 5. Surgical approach. A fairly large branch of the splenic artery was found running into the apex of the diverticulum in both cases. This is of interest from the standpoint of etiology, both as a factor of intrinsic weakness in the gastric wall and as an element of traction.

Figures 4 and 5, reproduced from "The American Journal of Surgery."

demonstrated (the radiologist will help you determine this), the surgical removal of the diverticulum should be considered.

Frequently, aberrant pancreatic tissue is found in the depth of the gastric diverticulum. However, this tissue usually is found in diverticula situated in the region of the antrum or in the prepyloric area (these constitute 25 per cent of all gastric diverticula), and not in those located near the junction of the lesser curvature of the stomach and the esophageal orifice (75 per cent). That is reasonable, because embryologically the first-mentioned area is more closely related to the pancreas.

Certain of these gastric diverticula also contain other neoplastic elements, such as schwannomas, neuromas of various types, adenomas, fibromas and even sarcomas.

DIAGNOSIS

Diagnosis is relatively simple and usually is made by the radiologist. He must be informed, however, that an examination of the upper stomach is necessary, and should be asked to do the examination in such a manner that it will be possible for barium to fill the diverticulum, if one is suspected. I stress this point because even in those patients who have careful barium examinations, approximately 5 per cent of the diverticula are not found. In this group, the ostium of the diverticulum frequently has an almost sphincter-like function. Some reports state that it actually has a sphincter; however, I feel that evidence for such a statement is lacking and that it is the normal muscularis around the ostium which contracts. In fact, during gastroscopic examinations you frequently can watch the ostium contract and relax, so you can see how it would be possible, especially in the presence of some gastric irritation, for the barium to enter the stomach and not the diverticulum itself. Radiologists who described cases of gastric diverticula which did not fill with barium even on re-examination (about half of the 5 per cent did not fill) reported that occasionally they did see an air bubble which subsequently was proved either at surgery or on postmortem examination to have outlined a gastric diverticulum. So even the radiologist cannot always make the diagnosis with certainty—at least a negative diagnosis. However, he can be of great help.

The first preoperative diagnosis of a gastric diverticulum was made by G. E. Brown in 1916. However, he diagnosed it incorrectly in that he called it an ulcer.

Gastroscopy is of value when there is doubt as to the diagnosis. In my estimation, gastroscopy permits quite a range of error in diagnosing lesions of the stomach—in attempting, for example, to differentiate benign and malignant lesions. Even the best gastroscopists are not going to have an average that is much higher than that of a competent radiologist. That statement may be unorthodox, but it is based on my own experience. However, in cases of gastric diverticulum, the gastroscopist usually can visualize the lesion because of its location—distal to the esophageal orifice and within 3 cm. of it—and make a definite diagnosis because he can observe the ostium, which is almost always round and has a definite, clearcut edge.

Usually no change is seen in the adjacent mucosal pattern, such as is observed in connection with an ulceration, unless there has been considerable inflammation; in other words, the normal folds of the stomach, the normal rugae, drop precipitously over the edge of the diverticulum into its depth.

Great care must be exercised in introducing the gastroscope. These diverticula sometimes are quite large and the tip of the gastroscope may fall directly into the diverticulum, causing perforation. If there is resistance in passing the gastroscope after it has passed the esophageal orifice, it is wise to check for position of the scope tip.

TREATMENT

The question arises whether medical or surgical therapy is indicated in cases of gastric diverticulum. Certainly at first these cases should be followed medically. It should be definitely determined that the diagnosis of gastric diverticulum is correct—in other words, the examination should be complete and every other possible cause for the symptoms eliminated. There should be demonstrable retention. Then, if the symptoms persist, there is reasonable assurance that good results will be obtained by removal of the diverticulum.

I want to describe briefly the 2 patients I mentioned previously. The first was a 45 year old woman who had a true gastric diverticulum. An oblique roentgenogram made after a barium meal showed a well defined outpouching of the stomach near the junction of the lesser curvature of the stomach and the esophageal orifice. The same amount of barium was present 24 hours after the first roentgenogram was made. This woman complained of vague epigastric distress. Her examination included a gallbladder series, and I also suspected a duodenal ulcer as the cause of her distress.

The second patient was a 19 year old girl. The location of the gastric diverticulum in her case was almost identical with that in the first patient. In both these cases, the diverticulum was removed by surgical means.

It should be noted that, since surgical procedures themselves may cause outpouchings which simulate diverticula, additional caution must be exercised in making a diagnosis of gastric diverticulum in a patient who previously has undergone surgery of the gastrointestinal tract.

In removing these diverticula, an incision is made in the gastrosplenic ligament. The spleen may be removed if there is fear of damage to it, or if better exposure is required. By lifting the stomach up, the diverticulum may be seen on the posterior surface. In both my patients, there were vessels branching from the splenic artery, going up and surrounding the gastric diverticulum, and the pathologist reported chronic inflammation with considerable round cell infiltration.

SUMMARY

The most frequent site of gastric diverticula is on the posterior wall of the cardia within a 3 cm. radius of the esophageal orifice at the junction of the lesser curvature of the stomach.

There is no definite syndrome associated with gastric diverticulum. However, the majority of patients complain of epigastric or substernal pain or a vague dyspepsia.

Diagnosis is made with the aid of the radiologist. Because the patient's symptoms do not constitute a familiar clinical entity, various roentgenographic and electrocardiographic studies are ordered to determine their cause. Then the radiologist may report the finding of a gastric diverticulum.

Medical management should not be continued if there is persistent barium retention in the diverticulum. Surgical excision will produce the best results under these circumstances.

Gastric diverticula, though uncommon, are described in this report because the men in the professional front lines who first see the patient with upper intestinal discomfort, vague dyspepsia or substernal pain should keep this diagnosis in mind.

DIAGNOSTIC CLINIC

PAROXYSMAL HYPERTENSION

GEORGE SAMUEL BOND*

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Paroxysmal hypertension is a fairly common clinical entity and is frequently overlooked. It is caused by either disturbances in the adrenal medullary function or a hypersensitive sympathetic nervous system. It is seen in several clinical types of different degrees of seriousness.

PAROXYSMAL hypertension is much more common than is usually realized, and yet in probably 75 per cent of the cases the real cause of the symptoms is not discovered. This is unfortunate, especially in view of the fact that when a correct diagnosis is made the treatment becomes so much more efficient.

I have a patient here today who represents one type, at least, of this condition. This 44 year old woman began to have headaches about 15 years ago. She went to various physicians, had her eyes examined, etc., without benefit. Her headaches came on periodically—usually beginning in the early morning hours, especially just after she got out of bed—and were accompanied by palpitation of the heart, cramps in the legs, and pains in the precordial area. After from one to several hours, the headache would subside.

This woman tried to enlist in the Women's Army Corps, but at first she was rejected because of hypertension. Her blood pressure was 240/130. However, the examining physicians were convinced that her hypertension was temporary, and she finally was admitted. During the last 10 years her blood pressure has averaged about 170 systolic. (To the patient): Do you know what the diastolic was?

PATIENT: It was 115 to 120.

DR. BOND: Periodically her blood pressure goes up to 240 to 250. She recently has had some swelling of the ankles. Physical examination shows the following: extreme apprehension and nervous tension; blood pressure 240/140; heart rate 125, apical impulse 10 cm. to the left of the midsternal line in the fifth interspace. The ocular fundi show little of significance. Neurologic examination is negative except for hyperactive deep tendon reflexes. Laboratory findings are essentially negative. A roentgenogram of the chest on September 26, 1951, showed a cardiac silhouette 7 per cent smaller than normal. The electrocardiogram showed a horizontal position.

The patient was hospitalized and given ½ gr. of phenobarbital twice a day. Her blood

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pressure gradually stabilized, and when she left the hospital it was 140/85. A BENODAINE® test caused a rise in the blood pressure, but it was noted that she had a marked rise even before the drug was injected. After the injection, a pressure of 210/130 was maintained for about 90 minutes.

G. S. BOND

This woman is representative of a class of patients frequently seen in general practice. In these cases, the blood pressure findings are all-important in establishing a diagnosis and, without them, various other diagnoses will be made, such as nervous states, hypoglycemia, palpitation and vasomotor disturbances.

Blood pressure is controlled primarily by two factors—namely, the resistance in the peripheral arterioles and the cardiac output. The latter is determined by the pulse rate and the amount of force and volume of the cardiac injection. In normal persons, a balance is struck between these two, so that the pressure is maintained at a certain level. Any variation either in output or in resistance will result in a change in pressure. If the resistance is increased and the output remains the same, the pressure goes up; if the resistance is decreased and the output remains the same, the pressure goes down. The reverse also is true: If the resistance remains the same and the output goes up, the pressure goes up, and so forth.

Renal factor—Certain substances excreted from the kidneys have either pressor or depressor effects on the blood pressure. These substances act directly on the arterioles, probably, and maintain the pressure at a balance. However, if there is an increase in secretion of the pressor substances, over a period of time that balance is raised so that the resistance of the peripheral vessels is increased and the blood pressure tends to go up. The renal factor almost always produces a permanent hypertension. It is not subject to fractional changes from day to day. Consequently, it is not often seen as a factor in cases of paroxysmal hypertension.

The sympathico-adrenal complex—Another factor which controls blood pressure indirectly is the sympathico-adrenal complex. The stimulus to the adrenals comes from the sympathetic nerves, which are acted on by various phenomena to bring about an increase in secretion from the adrenal cells. This sympathetic control is well illustrated by the fact that, if you section the sympathetics in that region, the secretion of the adrenals is lessened or stopped. This adrenal secretion acts on the arteriolar effector cells and brings about a tendency for an increase in pressure. The arterioles contract everywhere except in the heart and muscles, but the balance of the arterioles is so great on the side of the pressor factor that, even though they dilate at these two points, the pressure tends to go up whenever there is too much secretion.

Mention also should be made of the secondary effects of adrenalin. It stimulates primarily the heart, resulting in an increase in both the frequency and the force of contractions and, therefore, raises the blood pressure and increases the heart rate and activity. Carbohydrate metabolism is increased as a result of adrenalin, and there is a definite change in the body chemistry.

Nervous factor—A third factor which controls blood pressure is a purely nervous phenomenon. It originates in the sympathetic system, which tends to act directly upon the arterioles and raise the pressure. The parasympathetics tend to hold the pressure lower, and a balance is struck normally between these two. However, if any reaction takes place on the part of either sympathetics or parasympathetics, the result is a temporary fluctuation in blood pressure.

Variations in normal blood pressure do not result from minor changes in the sympathetic system. Major effects such as those caused by emotional disturbances, however, stimulate the sympathetics and tend to produce a marked increase in pressure. Compensatory factors are present to minimize this stimulation: In the circulation, there are the stretch receptors, such as are seen in the carotid sinus, in the arch of the aorta, and in the mesenteric vessels. Whenever the pressure rises as a result of sympathetic stimulation, these stretch receptors bring about a decrease in the cardiac output, thus neutralizing the effect of the hypertensive action. These

compensatory factors tend to maintain the pressure in a state of balance unless the sympathetic stimulation is too great. In our patients with purely nervous hypertension of a paroxysmal nature, we see the tremendous imbalance of the whole nervous control, with a tendency of the pressure to fluctuate back and forth as one system or the other gets control.

Chemical factor—A fourth factor, which I will not discuss in detail, is the chemical factor. This is due probably to changes in oxygen saturation, affecting the central nervous system and the brain. In these cases, where asphyxia takes place, there is a tendency to stimulation through the sympathetics, so that there is vasoconstriction and, although the stretch receptors may hold the pressure down, a consequent rise in blood pressure. However, under these conditions there are two factors that tend to slow the heart—namely, the stretch receptor factor and the direct vagus stimulation. These tend to lower the pressure and equalize the situation.

Another factor in the control of blood pressure is one that I will mention only briefly. In one phase of the action of the sympathicoadrenal system, the cortical section of the adrenals sometimes apparently is influenced by the hypophysis and can control the adrenal secretion. This is the case in Cushing's syndrome.

CAUSES OF PAROXYSMAL HYPERTENSION

In essential hypertension with a renal factor background, there are periods when the nervous factors predominate, i.e., they override the condition already present and produce a paroxysmal hypertension. In such cases, you will have patients who are getting along normally until certain crises increase their blood pressure from 170 or 180 to 250, 260 or 270. Along with this increase, some cerebral involvement usually will be found manifested by paralysis, unconsciousness, coma, etc. It is difficult in such patients to determine whether the paroxysm of hypertension was the primary cause of the symptoms or whether it resulted from the brain condition.

Probably one of the most important causes of paroxysmal hypertension is pheochromocytoma. These tumors, arising in the adrenals or in the chromaffin system, tend to stimulate the amount of adrenalin or epinephrine found in the circulation, and to produce violent symptom complexes, paroxysmal in type. About 70 per cent of these patients present cases of permanent hypertension, and the bulk of the patients in whom the diagnosis of pheochromocytoma has been made are those in whom a permanent hypertension is in effect. Thirty per cent, however, have a paroxysmal type of hypertension. Probably the determining factor (it is not definitely known as yet) is the fact that, in permanent forms of hypertension, adrenalin seems to be the predominant factor in the tumor secretion; in the paroxysmal type, adrenalin itself apparently is the predominant substance which produces the attack. In consequence, when you deal with the paroxysmal types of hypertension in patients with tumors of this class, you are apt to see many of the side effects and symptoms caused by adrenalin which you would not see in the permanent form of hypertension caused by a pheochromocytoma.

These tumors usually produce rather profound symptoms, because the adrenal content in most instances is so much higher than that found in normal persons. Analyses of the amount of adrenalin in these tumors show that in many it ranges from 3 to 50 times that found in the normal adrenal cell. Consequently, even slight stimulation produces a tremendous effect.

In about 1 of every 10 patients, these tumors are not found in the adrenals, but in other sections of the chromaffin tissue in the abdomen or even in the thorax. Often these cases are not diagnosed, simply because the tumor cannot be found either diagnostically or by surgery.

In studying the problem of pheochromocytoma, I was impressed by the number of patients who were thought to have tumors of this class and who were operated on without finding a tumor. So I wondered whether there may be other factors producing a picture identical with that seen in pheochromocytoma, yet without a tumor being present. There are two other possibilities: This may be an action of a hypersensitive adrenal or it may be an overactivity of sympathetic stimulation of the adrenals. We know that is possible, because we do see functional activity of adrenalin in fright, shock, and so on. Therefore, in many patients with hyper-

sensitive adrenals that will secrete under lesser provocation, stimulation may produce the typical picture of a paroxysmal hypertension with all the factors of a pheochromocytoma but without the presence of a tumor. It is purely an adrenal hypertension.

The next possibility in this problem is that of a purely nervous condition in which the patient has a hypersensitive sympathetic mechanism which acts by direct stimulation of the sympathetics on the arterioles themselves—and not through the adrenal secretion reacting on the arterioles—thus producing paroxysmal hypertension. These conditions often occur in tabes, eclampsia, thalamic tumors, lead poisoning and many of the emotional states.

Those four conditions constitute the possibilities behind the production of paroxysmal hypertension, and when such a patient is seen each condition must be considered in order to find the possible cause and to plan the course of treatment.

In contrast to the crises seen in cases of essential hypertension, which come on gradually, reach a peak, and then gradually subside, the attacks of paroxysmal hypertension occur very rapidly and without warning, and last from a few moments to several hours. In many cases, no cause can be found for their occurrence. Excitement, emotional states, pain and eating are all factors. The patient here today represents a common finding in many of these cases—the occurrence of an attack early in the morning.

CLINICAL FORMS OF PAROXYSMAL HYPERTENSION

These patients can be divided into four different classes: (1) those who have mild attacks; (2) those with symptomatic attacks; (3) patients who have paroxysmal hypertension associated with pulmonary edema; (4) patients with anginal tendencies.

In patients with mild attacks of paroxysmal hypertension, there is a pressure instability which causes variations in pressure as a result of various emotional stimuli, but the attacks are almost symptomless. However, these patients usually have two symptoms to a minor or major degree. Headache is very common, no matter how mild the attack may be. Vertigo is another common symptom, as is palpitation. These three symptoms often are not severe enough to point to hypertension as their cause, and thus many patients do not even have their blood pressure recorded.

The second group of patients are those who have symptomatic paroxysmal hypertension. The blood pressure may go as high as 350 systolic and 180 or 200 diastolic. Between attacks, the blood pressure often is normal or, as in the patient I presented, there may be a latent blood pressure which averages slightly above normal levels. These patients may have only a few symptoms localized in one tract, or they may have multiple symptoms. One of the most distressing of these is palpitation. In some instances, this is so severe that the chest wall can be seen palpitating underneath the clothing.

Nearly all these patients have dyspnea during attacks. Headache is almost always present and may remain even after the pressure has returned to its average level. Other symptoms include local pains, cramps in the legs, colic, throbbing vessels, epigastric pain, vomiting, nausea, a sense of jitteriness and uncertainty.

The patient usually is pale and his skin often is cold and clammy. Red splotches sometimes can be seen over the body in the pale areas, indicating vasomotor instability. The pulse may be fast or slow, but most often is fast.

These symptoms may be mistaken for a great many nervous or neurogenic situations and the real cause—paroxysmal hypertension—may not be realized.

An important form of this condition is paroxysmal hypertension associated with pulmonary edema. This association is seen in patients who have little or no hypertension but who have considerable myocardial insufficiency. Most often this insufficiency is caused by coronary disease—not necessarily coronary thrombosis and infarction, but by coronary insufficiency. When these patients have a paroxysm of hypertension, they go into sudden heart failure. Their chests fill with fluid very rapidly. During the attack, the blood pressure may be low or there may be no demonstrable pressure. Just before the attack, before the development of pulmonary edema, the blood pressure is very

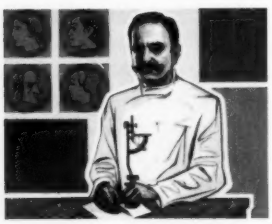
high. One of my patients, just prior to his attack of sudden heart failure, had a blood pressure of almost 300 systolic with a diastolic pressure of 180. During his attack, his pressure was 80/40. The important point to bear in mind is this: It is the paroxysmal hypertension which is precipitating the heart failure, and by preventing the paroxysms you can also prevent the acute heart failure with pulmonary edema.

The same may be true of patients with anginal tendencies. Frequently there will be no apparent cause for the anginal attacks, but in reality they are provoked by a paroxysmal hypertension. You have to examine the patient before he has an attack in order to ascertain that you are dealing with paroxysmal hypertension, because, as I mentioned previously, the hypertension is not demonstrable during the attack.

Lastly, patients go into shock suddenly, with all the picture of shock, and this is the subsequent event of a paroxysmal hypertension. After the attack, there is no evidence of hypertension.

Here is a group of patients who are suffering from many types of symptoms, some mild, some serious, some resulting in death. On the surface, these may look like ordinary situations, but behind many of them is a preliminary paroxysmal hypertension which has precipitated the attack and which has brought on the whole symptom complex.

OLD AND NEW TECHNICS IN PLASTIC SURGERY



ALTHOUGH COMPARATIVELY little has been written in English-language publications about Professor Jacques Joseph, he is often described as the leader of modern rhinoplasty. Dr. Joseph (1865-1934) lived and worked in Berlin and probably achieved his greatest prominence during and following the first World War. He had long interested himself in plastic surgery and had developed a unique method of operating within the nose so as to leave no external scar. He also introduced an operation for complete reconstruction of the ear by implanting an ivory ear which was covered by a skin flap.

The protractor-like instrument held by Dr. Joseph was developed by him to calculate the proportions of the nose in relation to its placement between the forehead and chin.

This month's cover painting by artist Edmund Kopietz illustrates early technics in plastic surgery, as well as the classification of four basic types of facial profiles.

Upper right is shown Tagliacozzi's rhinoplastic technic in which the graft was taken from the left upper arm, over the biceps muscle. The surgeon raised the skin by means of a pair of odd, broad-bladed forceps. Tagliacozzi (1546-1599) was the first surgeon whose name was associated with rhinoplasty, although the correction of deformities of the nose was practiced as early as 1440.

The sketch in the lower left-hand section of the cover is a representation of Ambroise Paré's technic for incised wounds of the face. Paré (1510-1590) was a military surgeon for many years and received a considerable part of his surgical training while attached to the French army.

DIAGNOSTIC CLINIC

ACUTE BACTERIAL PNEUMONIA

WILLIAM BARRY WOOD, JR.*

Washington University School of Medicine and Barnes Hospital, St. Louis

The case of a 45 year old man with type II pneumococcal pneumonia and bacteremia is briefly presented, and the pathogenesis, mechanism of recovery, and treatment of acute bacterial pneumonia are discussed.

THE patient I wish to describe is a 45 year old man who was well until 18 hours before admission to the hospital. He first noticed aching in the muscles of his arms and legs and two hours later he had pain in the lower right side of his chest anteriorly and in the right upper quadrant. This pain was made worse by deep inspiration. His temperature was 103° F. A few hours later he had a shaking chill and began to cough. The following morning he came to the Washington University Clinics. On examination he was found to have signs of consolidation over his right lower lung field, and a Type II pneumococcus was identified in his sputum. His white blood cell count was 15,000. He was promptly admitted to Barnes Hospital.

Past history was noncontributory. On admission his temperature was 39° C., his pulse rate was 100 and number of respirations per minute varied between 20 and 24. His blood pressure was normal. Roentgenograms showed consolidation over the right lower lung field, and many crackling rales were heard. His sputum was blood-streaked and he complained of pain in the right side of his chest.

Electrocardiographic examination was negative. The abdomen was not distended and there was no evidence of meningitis. Laboratory data showed no anemia, but the white blood cells numbered 15,100 with a marked shift of the differential to the left. Urinalysis was negative. The sputum showed the Type II pneumococcus previously identified in the clinic; there were 20 colonies per cubic centimeter of blood.

Penicillin therapy was started immediately; 100,000 units of aqueous penicillin were administered every three hours for seven days (total dosage of 800,000 units a day). At the end of this time "fortified" penicillin was given, 400,000 units every 12 hours. Within 36 hours his temperature was normal, although there was a slight secondary rise. A roentgenogram taken on the eighth hospital day showed clearing of the lesion in the right lower lung field. His white blood cell count returned to normal.

An interesting finding in this case was the course of the bacteremia. Before treatment, this patient had 20 colonies of Type II pneumococcus per cubic centimeter of blood. Thus the total number of organisms circulating in the blood stream would be about 100,000. Twenty-five minutes after the first injection of penicillin the colony count had fallen to 7, indicating that there were only 35,000 organisms in the blood stream; 10 minutes later the count had fallen to 3, and after 45 minutes no colonies were demonstrable in the blood culture. In other words, after less than one hour of treatment

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there was less than one colony per cubic centimeter of blood or a total of less than 5000 circulating organisms.

W. B. WOOD, JR.

Today is the tenth day of treatment for this patient, and he is well enough to come down to this meeting. This prompt response is familiar to all of you who have seen patients with acute bacterial pneumonia.

I would like to analyze the cellular physiology of the underlying infection in cases of bacterial pneumonia. This analysis will be based on experimental studies, most of them carried out in laboratory animals; nevertheless the clinical analogies which I shall draw are, I believe, valid.

The patient just described undoubtedly acquired his pneumonia by aspirating mucus infected with the Type II pneumococcus from his upper respiratory tract. Let us consider the lesion that developed in his lung, its histologic appearance, how it spread through the right lower lobe, the cellular mechanisms involved in the clearing of the lesion and in causing the remarkably rapid clearing of the blood stream. A feature in the microscopic picture of the pulmonary lesion which I would like to emphasize is the outer zone known as the edema zone, where all the alveoli are filled with edema fluid. On microscopic examination, this fluid is seen to contain many bacteria which grow freely and are washed into new alveoli through the interalveolar pores of Kohn. The spread of the injected fluid is accelerated by the respiratory movements of the lung. In the more central portion of the lesion there are still organisms, but here the fluid is replaced by polymorphonuclear leukocytes. These cells, of course, emerge from the alveolar capillaries. When heavier consolidation occurs in the center of the lesion, each one of the alveoli literally becomes a small bag of pus with leukocytes crowding the entire alveolar space.

It is important to emphasize that in such a lesion there are all phases of inflammation. Most of the bacteria are found in the edema zone where they multiply rapidly. The spread of the pneumonic lesion is quite like that of a grass fire which burns briskly at the periphery, leaving a burned-out area in the center.

Why are these particular organisms pathogenic to the lung? Many bacteria can be aspirated without causing pneumonia. Only a few species cause acute pulmonary infections in man. These organisms have one thing in common, i.e., the presence of a capsule which serves as an armor against the phagocytic cells. Leukocytes are unable to ingest fully encapsulated organisms suspended in fluid. In contrast, when antibody is present (which in pneumonia does not appear until the fifth or sixth day) it coats the outer capsule of the cell, and then the pseudopod of the leukocyte, whenever it comes in contact with the organism, is able to ingest it immediately.

Fortunately there is another mechanism of phagocytosis in the body that operates in the absence of antibody. If this mechanism were not present, it would not be possible to obtain such prompt responses to chemotherapy in the pre-antibody stages of the infection. This non-antibody phagocytosis has been termed "surface phagocytosis." In one form of this mechanism, the leukocyte traps the organism against the alveolar wall, and in this way is able to take it into its cytoplasm. In the second form the organisms are trapped between two or more leukocytes and thus are phagocytosed. These two phagocytic mechanisms which operate in the lung have been shown to be very important in clearing the alveoli of infective organisms.

A more complicated situation is present in the blood stream. The bacteria invade the blood stream from the lung, being carried there by lymphatics which empty into the subclavian vein via the thoracic duct. As soon as organisms enter the blood stream many of them are destroyed by phagocytic cells contained therein, particularly the reticulo-endothelial cells of the liver and spleen. Also, the polymorphonuclear leukocytes play an important role in small vessels all over the body. In the absence of organisms, the leukocytes in the circulating blood do not stick to the capillary wall; however, after bacteria have entered the blood stream, these leukocytes become adherent to the capillary

endothelium. When this occurs, the leukocytes may become motile and thus be potentially phagocytic.

Phagocytosis in the blood stream takes place in those capillaries where the blood flow is slow, for obvious reasons. Bear in mind that at any given moment many capillaries of the body are closed off, the blood in them being in a stagnant state. This phagocytosing process is going on all the time in the blood stream during bacteremia, there being a constant battle between phagocytes and multiplying organisms.

There is a third form of surface phagocytosis which sometimes occurs, in which organisms caught in a clot or small thrombus are phagocytosed by cells entering the interstices of the fibrin mesh.

From the foregoing discussion it can be seen that the cellular defenses of the body are extremely active during the course of an acute bacterial infection. It should be re-emphasized that all the phagocytosis demonstrated in these experiments took place in the absence of antibody. In the patient described previously, I am sure that the leukocytes were performing in a similar manner during the acute phase of his illness, when certainly no type-specific antibody could have been present in his blood stream.

What is the effect of chemotherapy in this situation? I think acute bacterial pneumonia should be considered an infection in which there is a delicate balance between the bacterial invasion and the cellular defenses that operate in the lung, in the lymph nodes and in the blood stream. If the patient receives no treatment there is a 3 to 1 chance that he will recover, indicating that the cellular defenses are fairly effective by themselves. On the other hand, if a chemotherapeutic agent is added which will slow down the multiplication of the bacteria, the recovery rate becomes much higher.

The most dramatic effect of chemotherapy is on the bacteremia, which clears very rapidly—blood cultures may become negative in less than an hour. In one patient with pneumococcal pneumonia, there were more than 1000 colonies per cubic centimeter of blood before therapy; one hour after penicillin was given, a culture showed no colonies in the blood stream. This astonishing recovery undoubtedly is due in part to the bacteriostatic effect of penicillin plus the cellular defenses of the host. It is also due in part, however, to the bactericidal effect of penicillin itself, the drug being able to kill some of the organisms outright. Further back in the lesion where the organisms are not growing rapidly and therefore are not susceptible to the killing effect of penicillin, the cellular defenses are called into play and cause destruction of the bacteria by phagocytosis.

What drug, then, should be used in the treatment of patients with acute bacterial pneumonia? There is a tendency today to use the so-called "shotgun antibiotics," and perhaps with good reason. They have a broader coverage and, when the diagnosis is not established with certainty, it is probably better to use such a drug. It should be emphasized, however, that these newer antibiotics are less potent than penicillin. They do not have the same bactericidal effect—they do not kill the organisms outright. Therefore, in very severe cases of acute bacterial pneumonia in which the organism can be identified it is better to use penicillin. If gram-negative organisms are suspected in the lesion as possible secondary invaders, streptomycin should be used also.

The over-all prognosis in acute bacterial pneumonia today was illustrated clearly by Dowling, who compared the mortality rate for patients who received no treatment (30.9 per cent) with that for patients who received serum treatment (16.9 per cent), sulfonamides (12.3 per cent) and antibiotics (5.1 per cent). This last figure indicates that 1 in every 20 patients with acute bacterial pneumonia will die. If the data are broken down further to consider only patients over 49 years of age, the mortality rate with antibiotic therapy is 15 per cent—1 in 7 patients. Therefore, these diseases continue to constitute an important cause of death. Every physician must consider them to be potentially dangerous and, whenever possible, patients with severe bacterial pneumonia should be hospitalized so that they can be given every benefit of therapy.

The photomicrographs shown during the presentation of this clinic may be found in the following references: J. Exper. Med. 73:201, 1941; 84:365, 1946; 86:239, 1947; 94:in press, 1952, and Science 106:86, 1947.

SYMPTOMATIC TREATMENT OF ECZEMA AND DERMATITIS

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For acute forms of dermatitis with edema and oozing, the symptomatic treatment is continuous, cool, wet dressings. Subacute to chronic forms need simple, soothing ointments. Chronic forms of dermatitis require stimulating ointments. In all forms, external irritants should be avoided and, in most, protection by bandages is needed.

SYMPTOMATIC treatment of patients with skin diseases that are variously called eczema or dermatitis is extremely simple in principle. Most of the preparations that are useful in the management of diseases of the skin are listed in the United States Pharmacopeia, the National Formulary, or similar sources.

For symptomatic treatment, dermatologic conditions fall into approximately three groups: (1) acute to hyperacute, (2) subacute to chronic, and (3) very chronic. Practically all the common varieties of eczema and dermatitis may present at one time or another any one of these three stages.

Acute dermatitis is characterized by edema, redness, vesiculation, oozing and crusting. The treatment of choice in practically all instances is cold, wet dressings applied continuously or semicontinuously. In some cases, these dressings may be required for only two to three hours a day, while other patients may need them 24 hours a day. This method of treatment is one of the dermatologist's most useful tools. As a rule, wet dressings are left open in order to obtain the added effect of cooling from evaporation, although at night they may be covered by an occlusive material such as paraffin paper or plastic cloth.

Half-saturated boric acid, 0.5 per cent Burow's solution (aluminum subacetate), or a very dilute potassium permanganate solution—1:2000 or 1:3000—may be used in these dressings. Concerning the latter, it must be remembered that potassium permanganate has a slight tanning action and may dry the skin excessively.

As the dermatitis subsides, it may be desirable to use simple ointments, creams or liniments during the intervals between the wet dressings. When this is done, the dressings may be placed right over the ointments.

Of the various stages of dermatitis, the subacute to chronic is the most common type seen in office practice. Generally speaking, this stage is characterized by lesions which are red and scaly, but not oozing or greatly thickened. As a rule, the ideal medication for this type would be a simple protective ointment such as zinc oxide ointment U.S.P., Lassar's paste (zinc paste U.S.P.) or some similar ointment or paste. Frequently, 2 per cent ICHTHYOL® may be added to

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the ointment, but other medications rarely are added. I believe that the greatest value of such medication in subacute to chronic dermatitis is that of simple protective action.

If the dermatitis is widespread, ointments may not be suitable, and simple creams are indicated. Calamine liniment N.F. probably would be as desirable as any. Treat these patients gently; give them time, and they often will recover.

In chronic cases in which the lesions are thickened and lichenified, the general therapeutic indication is for the stronger types of ointment. There are innumerable products which can be used; however, if you learn to use a few of the simple types well, you need not have an extensive formulary. As a rule, the standard ointment of the stimulating type that might be indicated in chronic dermatitis would be a crude coal tar ointment such as crude coal tar ointment U.S.P.

Two factors which are as important as local therapy in treating patients with eczema or dermatitis are avoidance of irritation and protection of the involved area. Avoidance of external irritation is an absolute necessity in all forms of dermatitis, whether acute, subacute or chronic. That means, as a rule, no soap and water and no detergents. Despite the fact that many detergents are widely advertised in the medical literature as being nonirritating, it is my impression that any detergent which cleanses is going to produce irritation in a case of dermatitis. So irritation from soap and water, detergents and all fat solvents such as turpentine, gasoline and the like must be avoided. This occasionally is extremely difficult. As a matter of fact, I rarely allow my patients to cleanse with oils or creams. I was taught that oils and creams could be used for cleansing, but it seems to me that the mechanical irritation and probably the physical irritation of even the simple oils such as vegetable oils, olive oil, cottonseed oil or mineral oil is harmful. Remember that avoidance of irritation is all-important in the management of eczema.

Protection of the involved area from mechanical and chemical irritation can be obtained in many ways. When continuous wet dressings are used, protection is automatic. In subacute and chronic conditions, however, protection in the form of bandaging—or, in infants, splinting—usually, though not always, is indicated. Bear in mind that the more the patient is protected from the trauma of rubbing, scratching and other major or minor injuries, the sooner his dermatitis is going to subside.

Internal medication for any patient with eczema or dermatitis is purely symptomatic, and probably the most efficient remedy for relief of itching is aspirin. Doses of 5 to 10 gr. every four to six hours will greatly alleviate the itching as well as the pain. In addition to aspirin, especially in the evening, it is desirable to use a sedative. This sedation may be provided by the use of one of the barbituric acid derivatives, either the quick-acting or the slow-acting form, in ordinary doses.

If sedation is necessary during the day, smaller doses of the barbiturates are useful. It is rarely necessary to give codeine or morphine derivatives.

The antihistaminic drugs are of value in only a few instances. Occasionally, in acute widespread eruptions, these drugs—particularly the types that tend to produce sedation—may be fairly good medication.

About four or five definite clinical syndromes constitute at least 90 per cent of the cases of eczema or dermatitis seen in office practice. Space does not permit my discussing all of them, but I will mention a few. The most frequent type seen, both in dermatologic practice and in general practice, is contact dermatitis, i.e., dermatitis caused by external irritants. Occupational dermatitis and poison ivy dermatitis are included in this group.

Another common form of dermatitis or eczema is a patchy dermatitis, of the back of the hand particularly, variously called nummular eczema, infectious eczematoid dermatitis, and other names. The allergic or atopic eczemas of infancy, childhood and early adult life are not as common as those already mentioned, but they are extremely difficult to manage.

I will discuss two types of contact dermatitis. The first, and most important, is therapeutic contact dermatitis, that is, dermatitis produced or aggravated by medication. I would estimate that at least one-fourth of the dermatologic patients I see in office practice have had their condition aggravated or even produced by ex-

ternal sensitivity to substances which have been used in treatment.

There are three groups of drugs that are widely sold, advertised and otherwise purveyed to the medical profession that cause trouble. The first is a group of surface anesthetics, almost all of which end with c-a-i-n-e. The "caine" group, which are similar to benzocaine, are common causes of therapeutic contact dermatitis. Second, there are the antibiotics, which are all potent sensitizers. Some of the newer antibiotics have not been in use for a long enough period of time to permit their evaluation, but if they follow the pattern set by penicillin there will be a considerable number of cases of therapeutic contact dermatitis resulting from the local use of antibiotics in treatment of skin conditions. The third and least common cause of therapeutic contact dermatitis, but that which produces some of the most severe cases, is the external use of antihistaminic drugs.

I would like to describe briefly some of the patients I have seen who have had therapeutic contact dermatitis. One woman developed a contact dermatitis over the genital area as a result of penicillin used for local treatment of pruritus. There was widespread eruption and aggravation of the pruritus. Another patient, a man who suffered with folliculitis of the beard, was treated with penicillin. In addition to the folliculitis, which did not subside, he developed a dermatitis as a result of penicillin sensitivity. I recommend that you do not use penicillin locally for such cases because if these patients develop skin sensitivities they are also sensitized if the drug is given internally. As I tell my students, don't sensitize a baby to penicillin because he has impetigo; when he is older, he may need the drug for treatment of a more serious condition.

Streptomycin is not widely used externally, but I have seen a patient in whom it caused a typical contact dermatitis of the eyelids. The patient was a nurse who worked in a tuberculosis sanatorium, and her hands came in contact with the drug.

Some of the antihistaminics are proving to be great sensitizers. In one case, a patient with chronic dermatitis had been treated successfully for about a year. However, within 24 hours after an antihistaminic drug had been applied he developed an acute dermatitis over the area, and a widespread drug type of eruption occurred. Another patient developed a generalized exfoliating dermatitis as a result of sensitization to antihistamines.

An example of local contact dermatitis, in this instance due to picric acid, was that seen in another of my patients. This type of eruption is quite severe, and formerly was seen quite often in connection with sulfonamide drugs. If such an eruption developed and if the patient subsequently took sulfonamide drugs, he would develop a generalized drug type of eruption.

Other patients with therapeutic contact dermatitis may be described briefly as follows: a case of dermatitis produced by one of the mercurials, MERTHIOLATE®; a case of poison ivy in which the patient used ferric chloride for treatment and developed ferric chloride dermatitis; a patient with sensitivity to dilute solutions of phenol; a case of true contact sensitivity to adhesive tape; an infant with generalized contact dermatitis as a result of sensitivity to an ingredient added to baby oil to make it antiseptic.

A patch test is the final step in the diagnosis of a therapeutic contact dermatitis. The worst offender is SURFACAINE®. Another is mercury and still another is EURESOL®, a common ingredient in scalp tonics.

The next group of patients I will mention briefly are those with occupational dermatitis of the hands and nummular eczema of the hands. These conditions can be acute, subacute or chronic. In determining the causative agent in cases of occupational dermatitis, it is important to know whether the individual is specifically sensitive to a substance that he contacts in his work or whether it is the result of primary irritation from substances such as soaps, alkalies, de-fatting agents, and the like.

The commonest type of eczema of the hands is that which occurs in patches. Both in cases of nummular eczema of the hands and in cases of occupational dermatitis of the nonspecific type, the most important factor in treatment is the avoidance of external irritation. In many cases this means that the patient cannot carry on his occupation, but it must be remembered that unless irritation is avoided, his symptoms will not be controlled.

DIAGNOSTIC CLINIC

MANAGEMENT OF MULTIPLE SCLEROSIS

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Multiple sclerosis, disease of exacerbations and remissions, more prevalent than any other neurologic condition except syphilis, is seldom lethal and not always a crippler. Although there is no cure, integrated application of suggested available types of therapy will give more symptomatic relief than can be obtained for many chronic diseases.

MULTIPLE sclerosis is a disease of the central nervous system which is characterized by exacerbations and remissions. It is not a rare disease, as is commonly supposed. Of the neurologic diseases, only syphilis occurs more frequently. The first complaints[1] often seem bizarre and only few objective abnormal findings can be demonstrated on careful examination. The symptoms frequently disappear spontaneously. An individual may have a number of attacks of transient numbness or paralysis before showing definite signs of organic disease of the brain or spinal cord. Approximately 1 patient in 12 with the disease may be expected to require institutional psychiatric help at some time.[2] In 1835 Sir Robert Carswell[3] described a pathologic specimen of the pons and cord spotted with grey areas of atrophy. About 30 years later Charcot presented a review of the literature and named the disease.

There are a number of etiologic theories,[4] among them being vitamin or mineral deficiencies, virus infections, emotional instability and glandular disturbances. However, during the last decade there has been a growing acceptance of the idea that allergy plays a major role in the etiology of this disease.[5-22]

The pathologic process in the chronic case consists of sclerotic patches scattered diffusely throughout both the grey and the white matter of the cerebrospinal axis.[23,24] These are areas of glial overgrowth in which the nerve fibers are usually preserved, at least to the extent that the axis-cylinders pass through, but are deprived of their myelin sheaths.[25] On the other hand, the recent plaques found at autopsy in the case of a patient with acute multiple sclerosis are not sclerotic; they are infiltrations by fluid of the nerve tissue surrounding blood vessels. These greatly resemble the changes seen in localized allergic edema.[26,27] The allergic theory as to the etiology in multiple sclerosis is based on these findings. This pathologic change is one of edema or urticarial wheals scattered throughout the entire central nervous system at various times.

The skin and the central nervous system originate from the same embryologic layer, namely,

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the ectoderm. Because of this, it is reasonable to assume that the entire central nervous system would be susceptible to the same allergic insults as the skin.

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When the urticarial wheals occur on the skin or along the intestinal tract, there is no serious damage as there is no pressure exerted. However, in a bony cavity such as the skull or vertebral column there is small room for expansion.[28,29] Therefore, through pressure the blood supply to certain areas is obliterated, and, if this pressure continues long enough, the destruction of tissue in these areas occurs with resulting scar tissue or sclerotic plaques. If the urticarial wheals disappear and the pressure is removed soon enough, the symptoms which have resulted from pressure disappear, and a remission results.

Careful studies of the degree of destruction within the plaques have given conflicting results. Putnam,[30] on the one hand, states that in a little more than 50 per cent of the plaques there is complete or almost complete loss of nerve fibers; Greenfield and King,[31] on the other hand, report that there is severe destruction in less than 10 per cent and that, in the remainder, little or no diminution in the number of axis-cylinders is found. This divergence is probably to be explained by the difference in technic employed. It is this persistence of conducting elements that accounts for the absence of tract degenerations in multiple sclerosis.

The three types of the disease are acute, remittent and chronic progressive. The remittent type may become chronic progressive. Prognosis depends on the type; it is very poor for the acute, rapidly progressive, and good for the other types. A hopeless prognosis should never be made. As Von Hoesslin[32] pointed out, the prognosis in cases of multiple sclerosis may by no means be as hopeless as many textbooks would lead one to believe. Substantial remissions, so complete that the patients consider themselves practically well, occur in a large percentage of cases.

Roughly about 50 per cent of all patients will be able to continue their usual occupations in a more or less reduced manner. Another 25 per cent will carry on partially with canes or crutches and only about 25 per cent will become wheel chair or bedfast cases. There should never be any bedfast cases. They can all be kept in wheel chairs, except that it is easier to care for them in bed than to get them into chairs. With proper symptomatic care, most multiple sclerosis patients will have a normal life expectancy. The disease is not the killer it has been pictured. Recent surveys at a large clinic have shown the survival rate of a large group of multiple sclerotics to be 95 per cent of normal for a five year period and 85 per cent of normal for a 10 year period after diagnosis was made.[33]

The number of persons with multiple sclerosis in the United States is thought to be about 300,000, about three-fourths of these living in the northern half of the country and about one-fourth in the southern half. The disease is a geographic one.[34] Outside the United States, Canada, British Isles and Northern Europe, there are few other places in which it is found. Allergists point out that in the countries where multiple sclerosis is most prevalent the people are eaters of cereals and dairy products, and sinusitis is also common. There is a general belief that dark-skinned persons or Negroes never have the disease. This is not true, as in the patients seen at our clinic there were 8 Negroes and 3 American Indians, all being clearcut cases.

Statistical data on our series of 1500 consecutive cases over a five year period are shown in Table 1. There were 680 men and 820 women in this series. The reason for this divergence in incidence by sexes is probably economic; i.e., the wife with multiple sclerosis is able to come and be treated, whereas it is difficult financially for the husband to leave his job to undergo treatment.

SYMPTOMS

Visual disturbances are often the first sign of the disease. There usually are scotomas, diplopia, optic neuritis, ocular palsies or independent ocular excursion.[35-42] There may be

optic temporal pallor, and blurred vision in one or both eyes. Charcot's triad of nystagmus, intention tremor, and scanning speech is often present, but frequently it is not found.

Many patients have a marked weakness or exhaustion. In most cases, tendon reflexes are increased while abdominal reflexes usually are absent. Past-pointing, emotional instability and gait disturbance—which may be either spastic, ataxic or a combination of both—are disabling at times. Bladder symptoms and constipation are common in multiple sclerosis.

Spasticity is the worst disabling factor; one or a combination of the four limbs may become paralyzed or uncontrollable. Choking and difficulty in swallowing are troublesome at times to a few patients.

There are episodes of paresthesia, numbness, incoordination, clonus, sensory change and pain. This latter symptom occurs in about 20 per cent of the cases. A few patients have convulsions. In an occasional case there will be vertigo, nausea and vomiting. At times the head or even the whole body may tremble. Babinski's and/or Romberg's sign may be present.

Most patients suffer from only a few of the aforementioned symptoms. Usually there is a temporary remission in some or all of the symptoms. However, usually they return, and remissions become shorter until at last the exacerbation continues. The case is then chronic progressive, and the patient's condition gradually becomes worse, with a physical decline to wheel chair or bed. Spinal fluid examination is of little aid in the diagnosis of multiple sclerosis, its only real value being to rule out syphilitic infection or space-displacing bodies. Pneumoencephalography may reveal evidence of nonspecific cortical atrophy. Spinal myelography may be necessary to exclude cord tumors or intervertebral disk herniation when no abnormalities appear above the spinal cord level.

There is no specific treatment or cure known for multiple sclerosis. Neither is there any known for many other chronic diseases. We do not cure tuberculosis, it is arrested; insulin only controls diabetes; and valvular heart disease is treated symptomatically. The following are procedures which should be attempted in cases of multiple sclerosis. Many cases can be arrested or retarded; all disabilities usually can be improved symptomatically and many times completely controlled. An early diagnosis is important. As in all other disease conditions, the sooner treatment is started the better for the patient.

TABLE 1

STATISTICS ON 1500 CASES OF MULTIPLE SCLEROSIS TREATED AT ST. JOSEPH HOSPITAL, MULTIPLE SCLEROSIS CLINIC

GEOGRAPHIC LOCATION			
Living in northern half of United States			1120
Living in southern half of United States			293
Living in foreign countries			87
AGE AT TIME OF FIRST SYMPTOMS	*Youngest*	*Oldest*	*Average*
Men	10	64	30.01
Women	5	49	28.43
AGE AT TIME OF ENTRANCE TO CLINIC			
Men*	17	69	41
Women	14	61	39.40
SEX AND RACE			
Men		680 (45.33 per cent)	
Women		820 (54.66 per cent)	
		1500	
White		1489 (99.26 per cent)	
Negro		8 (0.53 per cent)	
American Indian		3 (0.20 per cent)	
		1500	

*The average duration of time between first symptoms and entrance to the clinic was 10.47 years for men, 10.57 years for women.

PSYCHOTHERAPY

Patients with multiple sclerosis usually are dependent individuals, even before their disease has become manifest. When the diagnosis is made and they learn for the first time the facts about the condition from which they are suffering, they become very perturbed. At this point they are looking for someone in whom they have confidence to guide them. This is the physician's opportunity. At this time psychotherapy is needed. It should be both supportive and constructive. Patients should be shown by statistics that nearly half of them will be able to continue working whether they have treatment or not; that if they only keep working and walking, with treatment most of them can stay on the job; also, that very few patients die of either multiple sclerosis or its complications. It is not

the killer usually pictured; neither is it necessarily the hopeless crippler. They should also be assured that, with proper exercise, muscle tone can be retained and nearly all contractures prevented, especially if they adhere to treatment.

Euphoria is supposed to be a characteristic of multiple sclerosis. I have not found this to be true. Only about 10 per cent of the patients in our series have had this mood. At least an equal number suffered from the severest types of depression. The others varied between these extremes. A great many persons who appear to be euphoric exhibit this state merely as a defensive mechanism to cover up their inner feeling of tension in regard to the general attitude of other people toward them and their fear of the future. They have a tendency to be overtalkative, cooperative and amiable toward their physician, hoping that he will do everything he can to help them out of their dilemma. If the physician assumes a hopeless attitude toward their future, they retire within themselves, their spirits dropping to a low point. This, of course, is an emotional trauma of the worst sort. In our clinic, we make every effort to meet patients more than halfway in friendliness and cooperation, using this so-called euphoric attitude as one of our best vehicles in psychotherapy.

Allergy management lends itself remarkably well to psychotherapy, as most of the exacerbations can be traced to allergic insults from physical factors, food and miscellaneous or emotional allergic episodes. When this is called to the patients' attention, they are relieved of their anxiety and this robs the disease of much of its fearfulness and uncertainty as to the future.

PHYSICAL THERAPY

Physical therapy is of great value in the chronic cases. Nonparalyzed, atrophic and weak muscles become functional again as a result of such therapy. Coordination exercises and muscle re-education are part of this program. Badly contracted limbs are straightened with hot packs, simple orthopedic procedures and braces. Various types of canes and crutches are useful in getting patients out of wheel chairs and walking again. However, several short rest periods during the day are beneficial and usually are necessary.

MUSCLE RELAXATION

As an adjunct to physical therapy, voluntary muscle relaxation is very important. The principal drugs used for this effect are PROSTIGMIN®, MYANESIN® and curare. In our opinion, the latter has proved to be the most valuable.[26] It is used in the form of d-tubocurarine in a repository menstruum of oil and wax injected deep into the muscle in doses varying from 7.5 mg. every fourth day to as much as 120 mg. daily. The drug has a prolonged action with constant effects lasting in different patients from 12 to 96 hours.[43,44] In optimum doses this medication relieves tremors, spasticity and rigidity in most patients and improves incontinence and frequency of urination and constipation.

The therapeutic effect of d-tubocurarine is merely symptomatic. Its administration must be continued, although dosage eventually is lowered gradually. We ordinarily begin with a dose of 0.25 cc. every day, increasing or decreasing by trial and error to the optimum individual dosage.

ACTIVITY

If exacerbations can be definitely prevented, the normal tendency of the disease is one of recovery.[46] Realizing this, we forbid all use of tobacco and direct patients to avoid chilling, accidents,[47] overexertion[48] and emotional upsets.[49] Female patients are told of the dangers of pregnancy[50,51] in multiple sclerosis. All patients are instructed to be cheerful and factual, to lie down frequently for short intervals, to develop interests and hobbies, and to keep walking and working—at least to do a little of what they can do every day.

HISTAMINE

The criterion of the success of any treatment of patients with multiple sclerosis should be the prevention of relapses.[52] An attitude of rejection in therapy is easy to develop in regard to this disease.[53] Because our treatment is based

on the assumption that allergy is the cause of multiple sclerosis, histamine becomes the medication of choice, as it is the common denominator of all allergic diseases.[27,54]

Horton and his co-workers[55,56] seem inclined to relate any recovery and improvement in disorders of the central nervous system resulting from repeated injections of histamine to vasodilatation. Vasodilatation is of great importance in the medical treatment of multiple sclerosis. The more common dilators are nicotinic acid given orally, ETAMON CHLORIDE® given intramuscularly, DICUMAROL® given orally, and histamine given by four different methods: subcutaneous, intravenous, iontophoresis, and repository suspension intramuscularly.

Horton has shown that histamine causes greater increase in blood flow to the central nervous system than does any other drug known.[57] Photographic records of the pulsations of the human brain indicated that the subcutaneous administration of 0.25 mg. of histamine base produced a 725 per cent increase in the amplitude of the pulsations of the brain, whereas the intravenous administration of an 0.0011 per cent solution of histamine diphosphate at rates ranging from 18 to 30 drops per minute caused a 300 per cent increase in the amplitude of the pulsations of the brain. In a comparative study, the intravenous administration of 50 mg. of nicotinic acid produced only a 65 per cent increase in the amplitude of the pulsations of the brain even though it caused the face to become bright red in color.

On the other hand, Ferraro[58] speculated on the beneficial effects of histamine as being the result of the production of histamine-specific antibodies. Kwiatkowski[59] has shown that all living tissue contains histamine except the central nervous system, motor nerves and sensory nerves from special sense organs. I am of the opinion that the dramatic improvement in acute cases and the improved condition of the chronic cases under histamine therapy are in some way related to this absence of histamine in tissues of the central nervous system. The reason for the effectiveness of this therapy will not be known until research gives us greater knowledge of the biochemical and immunologic factors involved.

Intravenous infusions—Following the establishment of a definite diagnosis, some form of histamine therapy is indicated for the balance of the patient's life. Five years of work have convinced us that the best foundation is laid with the standard histamine intravenous infusion of 2.75 mg. of histamine diphosphate in 250 cc. of normal saline given at a rate of 30 to 60 drops per minute, taking 90 minutes for the dose.[57,60,61] We now routinely give 30 such doses as the basis of our multiple sclerosis course, 5 each the first three weeks, 3 each for the next five weeks.

At times, in serious acute cases, a continuous infusion[62] of 11 mg. of histamine diphosphate in 1000 cc. of normal saline at a rate of 30 drops per minute every six hours is given, alternated with 11 mg. histamine diphosphate in 1000 cc. of 5 per cent glucose solution. This continuous infusion is continued for periods of 24 to 48 hours as tolerated.

In our series we have administered histamine diphosphate intravenously over 60,000 times with no noticeable reactions, even from patients reporting earlier histamine reactions or failures. We believe that reactions are due to the pyrogenic factor of improper sterilization or to the histamine being administered too rapidly, and that failures result when too little histamine is given for too short a time, or when it is given too late—obviously, irreversible changes cannot be corrected—or when its administration is accompanied or followed by the use of tobacco, one of the strong vasoconstrictors.

Iontophoresis—Abramson[63-68] developed the technic for administering histamine by iontophoresis. This method is very simple, involving only the passage of histamine into the skin, driven by a galvanic current which forms deposits in the pores of the skin. Under the electrode area a large wheal is formed containing histamine, which is slowly absorbed.

The principal advantages of histamine iontophoresis are as follows: It is well adapted for home use; the apparatus is inexpensive and sterile equipment need not be employed; for regular administration its results compare favorably with the intravenous method, the flush being similar, the venous oxygen content superior and the absorption obviously extended.

Subcutaneous—The subcutaneous injection of aqueous histamine is well known, but seems to us to be superseded by the superior methods of administration by iontophoresis and repository intramuscular injection.

Repository suspension—For the past two years we have been using a repository histamine suspension for home treatment. This method is even more simple than iontophoresis. We use histamine diphosphate, 2.75 mg. per cubic centimeter in a menstruum of peanut oil and oxycholesterol derivatives.* This medication is given deep intramuscularly daily, as insulin is given in diabetes.[69] The first dose is usually 0.05 cc., and this is increased as tolerated until 0.50 cc. is given daily. The increase should be a slow process, never more than 0.05 cc. at a time. We found that with this medication the venous blood oxygen content remained at the arterial level for over 48 hours in most cases.[70] This indicated marked vasodilatation for that period of time.

Brickner and Franklin,[71-72] in 1947, stated that the basic notion in the therapy of multiple sclerosis "calls for continued vasodilatation of the vessels of the nervous system, as well as for the prevention of spasm. Both these measures should be enforced for 24 hours a day. A drug-free interval of even a few minutes would suffice for an attack." Repository histamine may fulfill these criteria of therapy.

ALLERGY MANAGEMENT

At our clinic, complete allergy management is the basis of therapy.[73] On all of our patients, allergy histories are taken and scratch tests are made for sensitivities to foods, epidermals, molds, fungi, pollens and miscellaneous allergens. Under this therapy, allergenic extracts are prepared for each patient as indicated, including respiratory vaccines for the typical "head cold" of multiple sclerosis noted by so many writers.[74,75]

Nearly all our patients give histories of some form of allergic sensitivity. Those with multiple food allergies are apparently most spastic, bearing out the generally conceded fact that foods are the worst offenders in cerebral allergies.[49,76,77] On the basis of scratch tests, diet diaries and elimination diets, a suitable diet is developed for each patient. Most of those presenting especially serious and difficult food sensitivities can be placed on Rowe's[78] cereal-free diet with good results.

Vitamins should be given as needed to improve general health. Lately, vitamin B_{12} in large doses is being given with reports of beneficial effects.

ENDOCRINES

Multiple sclerosis patients typically show hormonal deficiencies, especially of the gonadotrophic hormones. The possible need for any supplementary hormones should always be considered by anyone treating patients with this disease.

Cortisone and ACTH are being administered extensively at the present time with undoubted success in some acute cases.

PRESENTATION OF PATIENTS

I would like to describe briefly the 5 patients with multiple sclerosis who are here today. First, this girl with a spastic gait. She can walk, but requires assistance, and has to turn her foot outward at the ankle. The next patient is a doctor from Ohio. He has a wide stance and a spastic gait. I would like to ask the doctor to say a few words so that you can notice the scanning speech.

PATIENT: I am g-g-glad to be here and I am enjoying myself very much. I have a l-l-little bit of hesitation in my talk.

DR. JONEZ: The next patient has a spastic ataxic gait, but he gets around very nicely. I don't know this man's history, but offhand I would say that he can continue working for the rest of his life and will probably die of heart disease or pneumonia or as the result of an automobile accident, rather than of multiple sclerosis.

The next girl has what we might call an unintention tremor. She has to hold her chin to keep her head from shaking. This, to me, is one of the most pathetic phases of multiple sclerosis. Sometimes these patients have to be tied in their wheel chairs to keep from sliding out. She is holding herself tight now.

*HISTAPON®, supplied through the courtesy of Endo Products, Inc.

Next I would like to show you a patient with spastic scissoring of the legs. This condition is so severe that she keeps a pillow between her knees to prevent the formation of ulcers. I don't know how long this girl has been ill, but I imagine she is bedfast. (To the patient): Is that right?

PATIENT: Yes.

DR. JONEZ: How long?

PATIENT: A year.

DR. JONEZ: I don't know who her doctor is, but I believe that this girl can and should be placed in a wheel chair at once.

COMMENTS AND CONCLUSIONS

After treating over 1500 patients on a private patient basis, it is our opinion that much can be done for the sufferers of multiple sclerosis. Early diagnosis and treatment result in a great possibility of bringing about a remission and the retarding or arresting of the disease. The defeatist attitude toward this ailment which is so prevalent in the medical world today is not justified. In all cases, when the diagnosis is made, every effort should be exerted to keep the patients' morale up and keep them from assuming a hopeless attitude. Physical therapy with a muscle relaxant should be used to keep muscle tone at a high level. Treatment as outlined does not cure, but it does arrest symptoms a great many times. Above all, it holds out hope to these patients with reference to their future. By this regimen we have made ambulatory or wheel chair cases out of bedfast ones. Also, we have taken wheel chair patients and made them ambulatory. Still others have become symptom-free and remained so without an exacerbation up to periods of over five years. This is far more than we are able to do for many other chronic diseases.

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MEETINGS AND POSTGRADUATE COURSES

Tufts College Medical School

For information on the courses listed below, address Postgraduate Division, Tufts College Medical School, 30 Bennet Street, Boston 11, Massachusetts.

Review of recent advances in internal medicine, October 6-11.
Proctology I, October 20-24.
Ophthalmology, Monday, Wednesday and Friday mornings, October 20-November 14.
Dermatology I, November 3-7.
Pediatrics I, November 3-7.
Pediatrics II, mornings, November 3-15.
Neuro-ophthalmology, November 17-21.
Electrocardiography I, December 1-5.
Hematology I, December 8-12.
Rheumatic diseases, mornings, December 15-19.

Congress of Neurological Surgeons

Second annual meeting, November 6-8, at the Palmer House, Chicago. Speakers will include: Prof. Herbert Olivecrona, Stockholm; Dr. Albert Kuntz, St. Louis; Dr. E. A. Hines, Rochester, Minnesota; Dr. Francis L. McNaughton, Montreal, and Dr. Harold Wolff, New York.

CLINICAL STUDY

TREATMENT OF MIGRAINE

With Special Reference to Ergotamine Tartrate-Caffeine Rectal Suppositories*

PHILIP E. ZANFAGNA**

Lawrence General Hospital, Lawrence, Massachusetts

Effective treatment of migraine continues to be a major medical problem confronting the physician. Thirty cases of migraine are presented in which a new form of treatment by means of rectal inserts has been used. Its effectiveness is reflected in the excellent results obtained.

THE migraine syndrome comprises a symptom complex of unknown etiology manifested by a periodic, unilateral headache associated with gastrointestinal dysfunction, a cortical disturbance, and/or a family history of migraine.

The basis of this report involves the treatment of proved migraine in 30 clinic and private patients. Of the 30 patients, 26 were women and 4 were men, consistent with the established fact that migraine is more frequent in the former group. At the time of this study 10 patients were receiving GYNERGEN® injections with good results; 10 patients were using CAFERGOT® or codeine tablets with fair results and 10 patients were undiagnosed. A typical attack of migraine was reproduced in the 10 previously undiagnosed cases by the sublingual administration of nitroglycerin, 1/100 gr. Each patient received a complete physical examination with a detailed history. All endocrine, allergic, metabolic or organic factors were eliminated as the cause of the headache.

PHYSIOLOGY AND ETIOLOGY

Although the specific etiology of migraine has not been demonstrated, there seems to be sufficient clinical evidence in all cases to suggest a common denominator: Tense, nervous, emotionally hypersensitive individuals with scintillating personalities are predisposed. Emotional stress and inner conflicts usually act as initiating or trigger factors.

It is imperative to understand the vascular pattern involved in the production of migraine for best therapeutic results with any drug.

It has been generally accepted that the immediate physiologic changes involve vasoconstriction of the branches of the internal carotid artery with resulting anoxemia and the preheadache aura. After a period of several minutes to hours, the second stage is manifested with dilatation of the intracranial branches of the external carotid artery and the throbbing headache. The unaborted attack of migraine may proceed to the third stage in which there is edema of the vessel walls and scalp, producing a steady, more generalized pain not amenable to treatment with any of the ergot derivatives or other drugs.

TREATMENT

It is obvious that specific treatment between attacks comprises the determination of psychogenic factors and mental stress and strain con-

*SUPPLIED AS E.C. 112 BY SANDOZ PHARMACEUTICALS DIVISION, SANDOZ CHEMICAL WORKS, INC., NEW YORK, NEW YORK.

**SENIOR STAFF, CONSULTANT AND CHIEF OF ALLERGY, LAWRENCE GENERAL HOSPITAL, LAWRENCE, MASSACHUSETTS.

TABLE 1

ADMINISTRATION OF ERGOTAMINE TARTRATE-CAFFEINE RECTAL SUPPOSITORIES IN 30 CASES OF MIGRAINE

TIME OF ADMINISTRATION	RESULTS		
	EXCELLENT[1]	GOOD[2]	POOR[3]
Within one hour after onset of headache	24	3	3
Within two to three hours after onset of headache	18	6	6
After three hours from onset of headache	8	8	14

[1]Complete disappearance of headache within two hours.
[2]Relief of headache resulting in no interruption in daily routine.
[3]Progression of intensity of headache.

ducive to attacks of migraine. Appropriate psychotherapy may be necessary to abolish the trigger mechanism. However, a patient with a migraine headache demands immediate symptomatic relief.

Good results have been reported[1-5] in aborting mild attacks by the use of cafergot tablets in sufficient doses during the phase of vasoconstriction or early vasodilatation. In my experience, most patients hesitate to take any medication until the onset of the headache which is usually accompanied by gastrointestinal disturbances, making oral medication impractical.

In this study, extending over a period of nine months, all patients were given rectal suppositories containing 2 mg. of ergotamine tartrate and 100 mg. of caffeine (E.C. 112). All patients were advised to use the suppository within one hour of the onset of the headache. Gynergen and dihydroergotamine methanesulfonate (D.H.E. 45) injections as well as all forms of oral medication were withdrawn. A second trial of the suppositories in which they were used within one to two hours from the onset of the headache was made in the same patients. In the third trial all patients were asked to wait for three hours after the onset of the headache before using the rectal inserts. Initially 15 patients were given rectal placeboes, but the negative results were so predominant that this procedure was considered unnecessary.

ANALYSIS OF RESULTS

Table 1 demonstrates the clinical results obtained with the ergotamine tartrate-caffeine suppositories. Excellent results as evidenced by the relief of headaches within two hours were seen in 24 of 30 patients using the suppository within one hour from the onset of the headache. Three had good results reflected in the amelioration of symptoms, enabling the patients to continue their duties. Three patients who had been using gynergen injections for approximately two years reported poor results. During the second trial when the suppository was inserted from one to two hours after the onset of headache, 18 patients had excellent results, 6 showed good results and 6 reported poor results. The suppositories showed less therapeutic response when used after three hours from the onset of headache: 8 had excellent results, 8 reported good results and 14 patients received no benefit. Similar good results with the rectal use of ergotamine tartrate-caffeine have been reported.[6,7]

Six of the 30 patients complained of an aggravation of nausea and vomiting accompanying the headache. These reactions were minimized when the 6 patients initially used one half of the suppository, inserting the second half after 20 to 30 minutes.

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SCIENTIFIC EXHIBIT

THE MYOFASCIAL GENESIS OF PAIN

JANET TRAVELL AND SEYMOUR H. RINZLER*

Cornell University Medical College and Beth Israel Hospital, New York

Trigger Areas in Myofascial Structures Can Maintain Pain Cycles Indefinitely

THE TRIGGER AREA

Data are drawn from about 1000 patients with (1) pain syndromes and (2) myofascial trigger areas.

The trigger area is a small hypersensitive region from which impulses bombard the central nervous system and give rise to *referred* pain.

Pain is set off whenever the trigger area is stimulated by pressure, needling, extreme heat or cold, or motion that stretches the structure containing the trigger area.

The resistance to stretching leads to apparent shortening of the affected muscle with limitation of motion and weakness.

High-intensity discharges from a trigger area may be accompanied by vasoconstriction and other autonomic effects limited to the reference zone of pain.

A trigger area at a particular spot gives rise to a similar distribution of referred pain in one person as in another.

This constancy of pattern indicates that impulses concerned in the unfamiliar reference of somatic (like visceral) pain follow fixed anatomic pathways.

This fact enables one to use a known reference pattern to locate the myofascial source of pain.

THE PAIN CYCLE

Myofascial trigger mechanisms may be initiated by direct trauma to muscle or joint, chronic muscular strain, chilling of fatigued muscle, acute myositis, arthritis, nerve root injury, visceral ischemia or dyskinesia, and hysteria.

Predisposing factors may be general fatigue, low metabolic rate with creatinuria, chronic infection and psychogenic stress.

Protracted myofascial pain following activation of trigger area is thought to depend on a reflex pain cycle maintained by the trigger area.

The pain cycle is often terminated permanent-

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ART WORK BY JULIUS F. KOCH AND MAISON C. CLARKE.

THIS INVESTIGATION WAS SUPPORTED BY A RESEARCH GRANT FROM THE NATIONAL HEART INSTITUTE, UNITED STATES PUBLIC HEALTH SERVICE, BETHESDA, MARYLAND.

THIS EXHIBIT WAS SHOWN AT THE ANNUAL (ATLANTIC CITY) SESSION OF THE AMERICAN MEDICAL ASSOCIATION, 1951.

ly by local block procedures with only transitory pharmacologic actions: procaine infiltration or dry needling of trigger areas, sustained heavy pressure on them, and spraying the overlying skin with ethyl chloride.

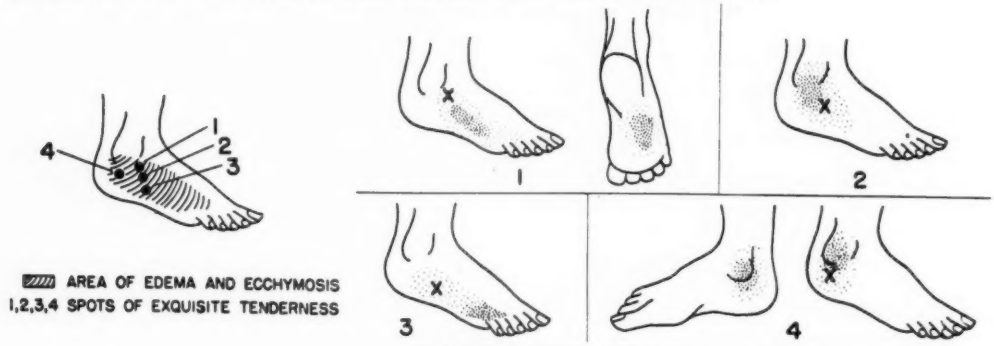
Efficacy of local block implies that the mechanism which set the pain cycle in motion is not the same as that which keeps it going. The pain cycle continues long after the precipitating cause has vanished.

After local block the pain cycle is reactivated if a remote lesion supplies a fresh stream of noxious impulses.

When local block relieves pain, no immediate deduction can be made from that fact alone as to the primary cause of the pain syndrome.

Trigger Areas Appear at Site of Trauma

ANKLE SPRAIN 44 HOURS AFTER INJURY IN 43 YEAR OLD WOMAN



The spread of pain does not follow any sensory nerve distribution, but represents referred pain which demonstrates trigger areas in the periarticular structures. No pain spread results from infiltrating nontender spots.

Trigger Areas Appear in Reference Zone of Visceral Pain

PATHWAYS OF NOXIOUS IMPULSES IN PAIN OF CORONARY ARTERY DISEASE

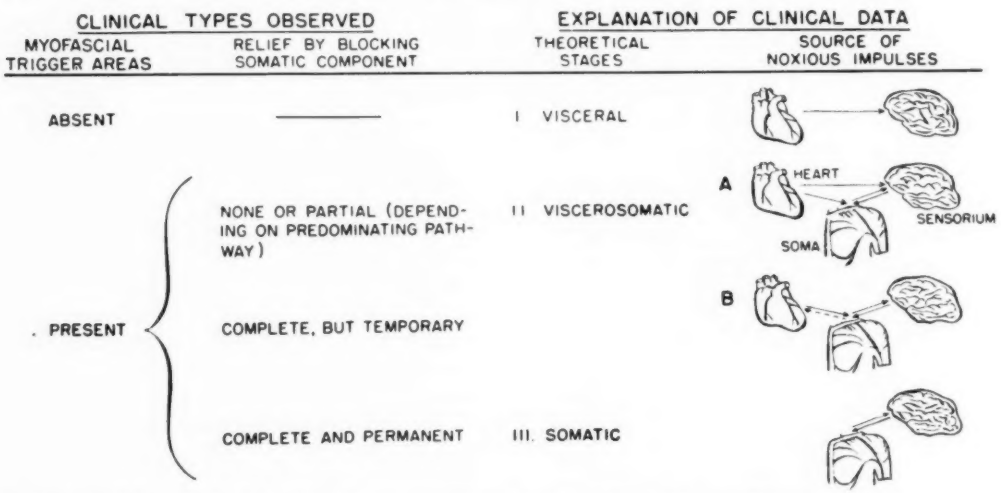
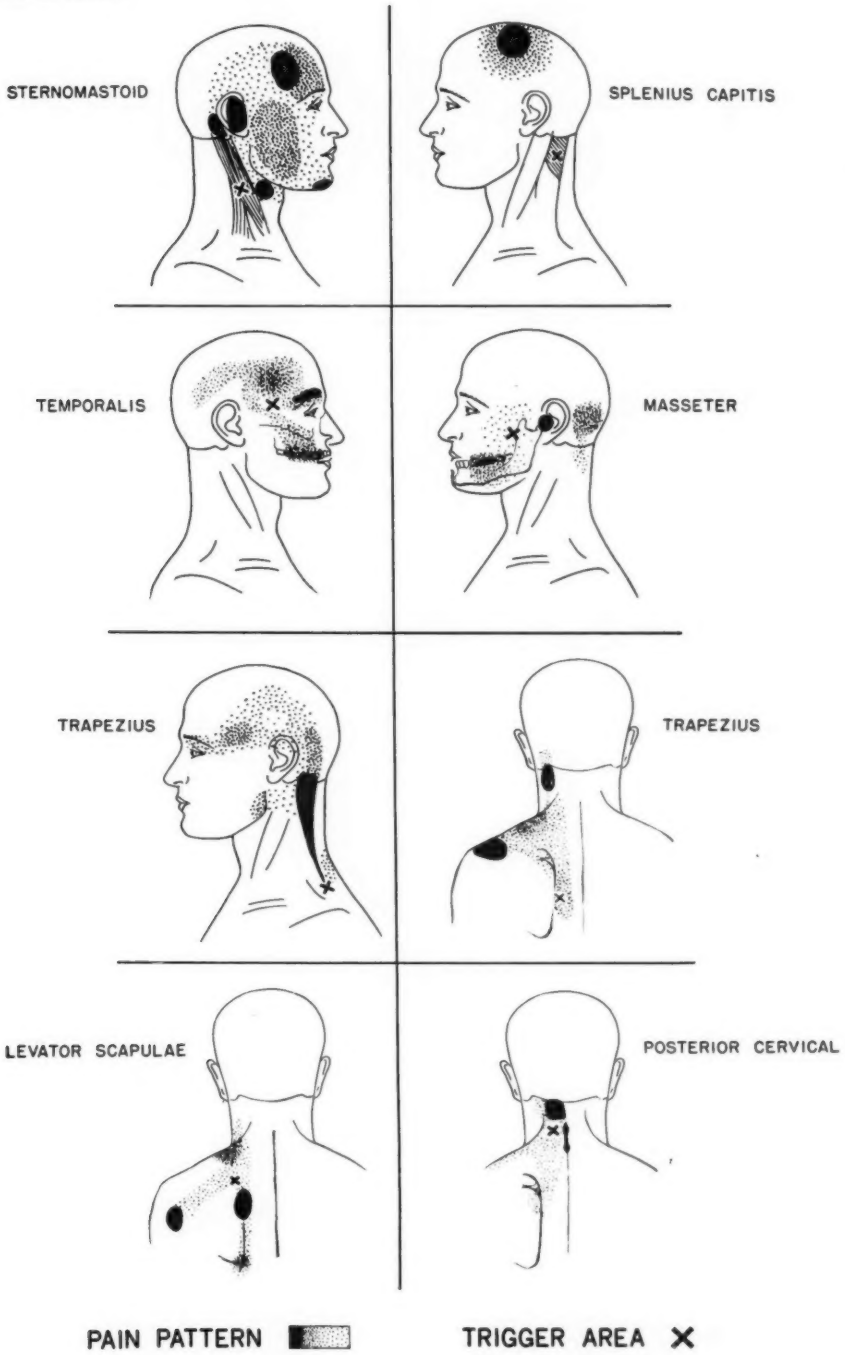
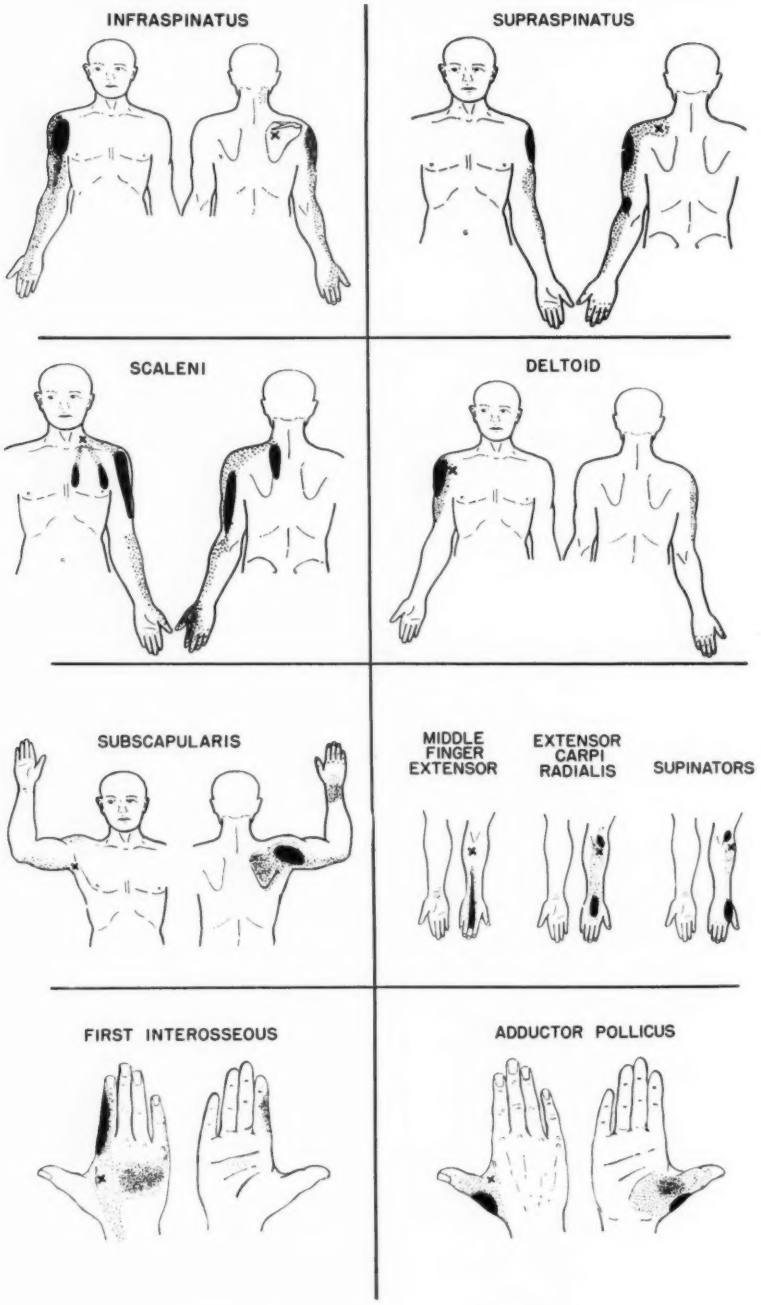


Diagram explains why local block of trigger areas in the chest muscles sometimes relieves cardiac pain.

Once the Pain Reference Pattern of a Muscle Is Known, It Can Be Used to Locate the Muscle That Is the Source of Pain

HEAD AND NECK




INFRASPINATUS
SUPRASPINATUS
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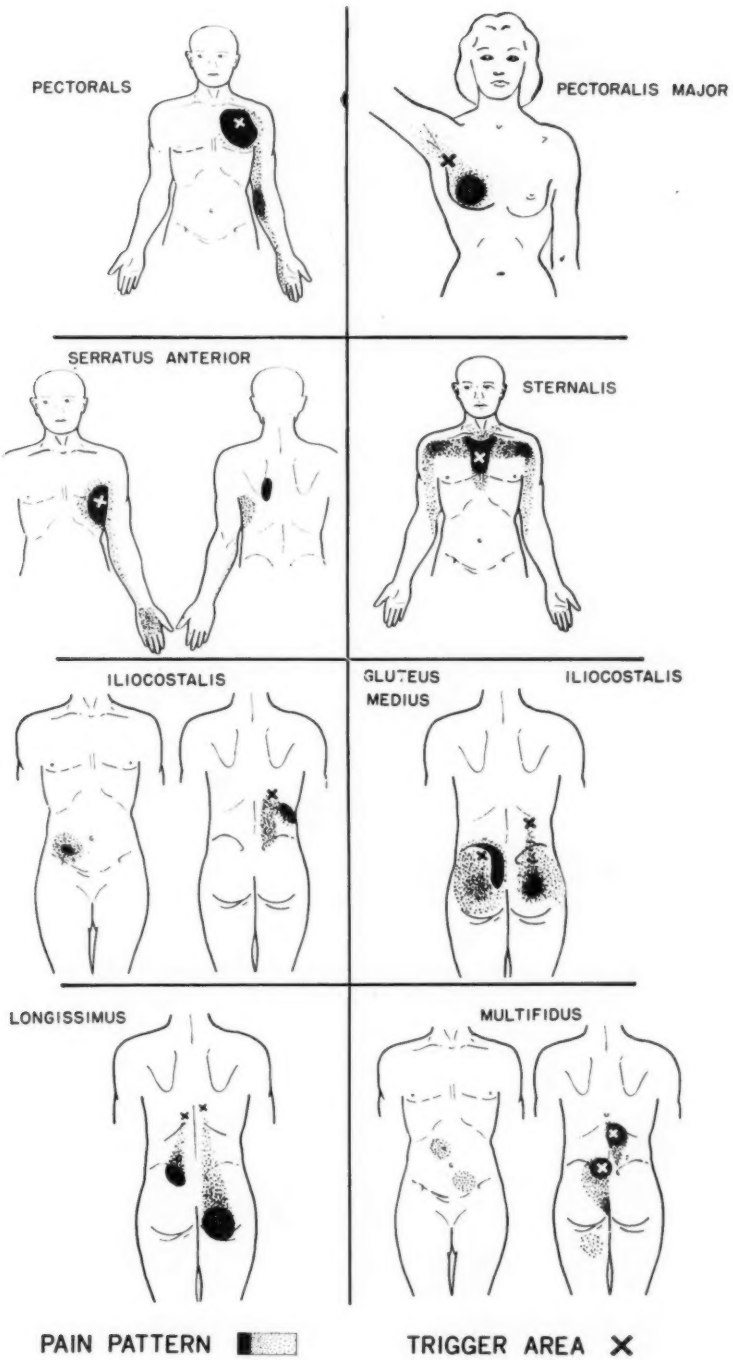
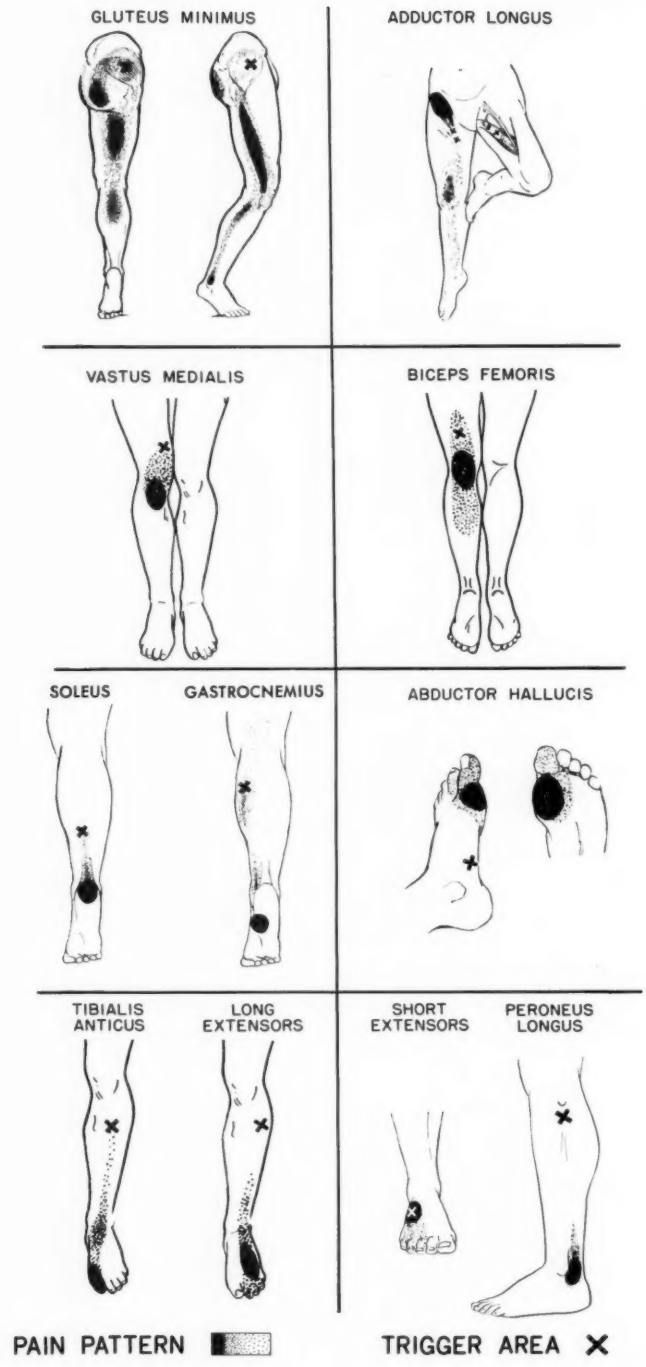
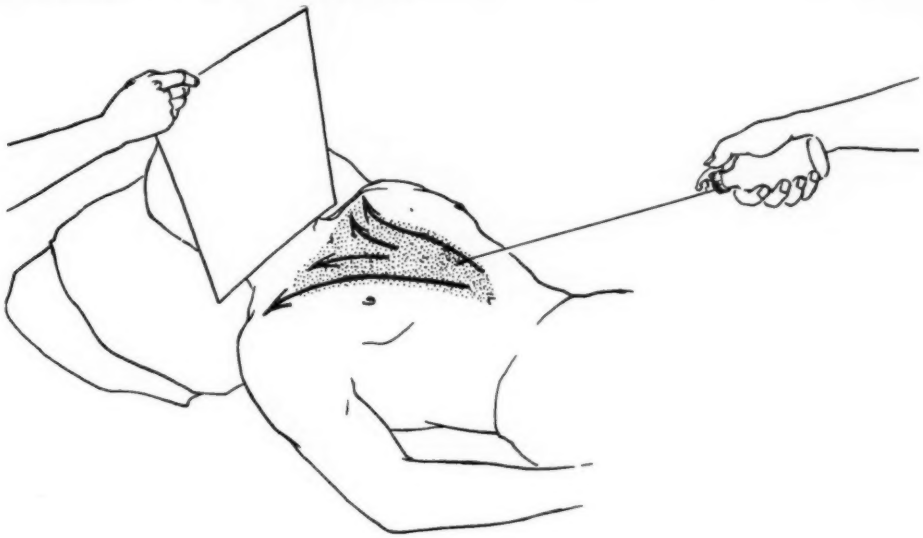
SUBSCAPULARIS
MIDDLE FINGER EXTENSOR
EXTENSOR CARPI RADIALIS
SUPINATORS
FIRST INTEROSSEOUS
ADDUCTOR POLLICUS
PAIN PATTERN
TRIGGER AREA ×


PECTORALS
PECTORALIS MAJOR
SERRATUS ANTERIOR
STERNALIS
ILIOCOSTALIS
GLUTEUS MEDIUS
ILIOCOSTALIS
LONGISSIMUS
MULTIFIDUS
PAIN PATTERN
TRIGGER AREA


GLUTEUS MINIMUS
ADDUCTOR LONGUS
VASTUS MEDIALIS
BICEPS FEMORIS
SOLEUS
GASTROCNEMIUS
ABDUCTOR HALLUCIS
TIBIALIS ANTICUS
LONG EXTENSORS
SHORT EXTENSORS
PERONEUS LONGUS
PAIN PATTERN
TRIGGER AREA ×

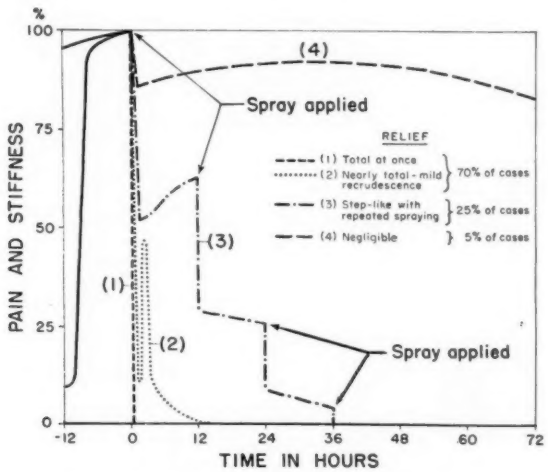
Transitory Local Block of Trigger Areas May Relieve Myofascial Pain Permanently

ETHYL CHLORIDE SPRAY PROCEDURE



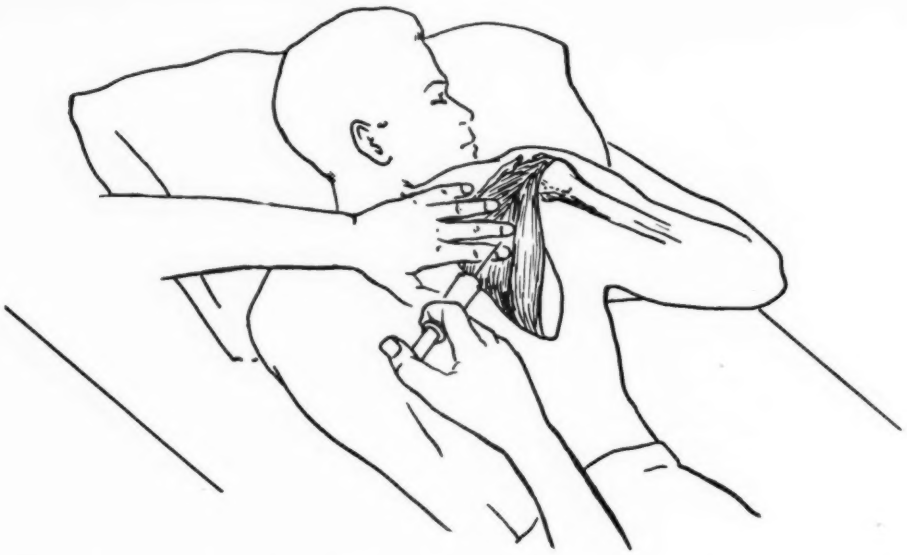
Guard against fire hazards.
Raise patient's head above level sprayed.
Hold container 2 feet away.
Start stream at trigger area, carry over reference zone.
Apply stream at acute angle.
Spray in one direction, with slow sweeping motion.
Repeat sweeps in rhythm of a few seconds on and off.
Lengthen interval between sweeps if aching develops.
Do *not* frost skin.
Stretch muscle by gentle movement.
Continue until pain disappears and tenderness at trigger area is less.
Stop if no effect in five minutes.

TYPES OF RESPONSES TO SPRAY IN 40 CASES OF ACUTE "STIFF NECK"



When there is little response to spraying, procaine infiltration may be effective.

PROCAINE INFILTRATION PROCEDURE



By pressing on trigger area, demonstrate pain reference to patient.

Ask patient to announce when pain radiation is felt during infiltration.

When needle hits trigger area, pepper region by moving it in and out of muscle, injecting 1 to 2 cc. continuously.

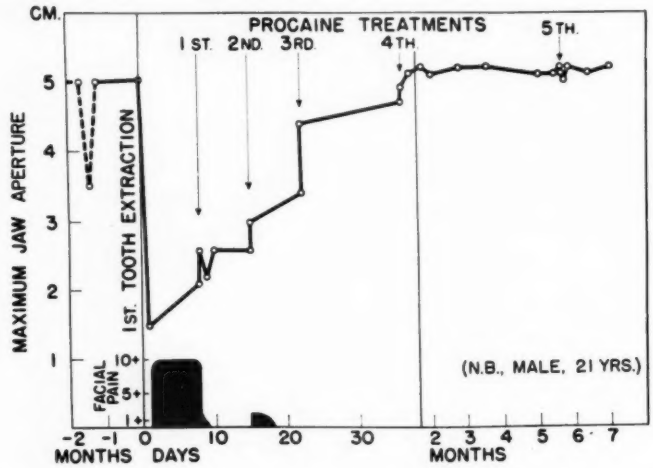
Use 0.25 to 0.5 per cent procaine hydrochloride in physiologic saline (unless history of procaine allergy).

Use a sharp 22 to 24 gauge needle, 1 to 3 inches long, depending on site of trigger area.

Apply hemostasis promptly.

Check success of injection. If trigger area is still tender, reinfiltrate at different depths and angles.

TYPICAL CLINICAL RESPONSE TO PROCAINE: CASE OF MASSETER SPASM AFTER TOOTH EXTRACTION

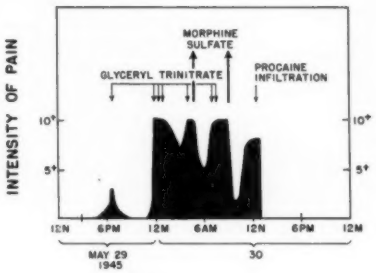


Dramatic relief of pain after first treatment. Step-like increase in range of motion with each treatment.

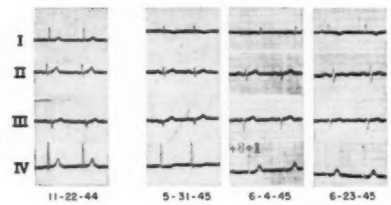
ACUTE MYOCARDIAL INFARCTION WITH SOMATIC COMPONENT

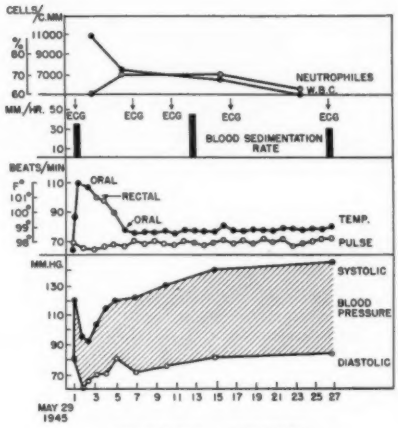
W. T. 73 YEARS OLD. AWAKENED BY INTENSE SUBSTERNAL PAIN RADIATING DOWN LEFT ARM. PAIN CONSTANT UNTIL RELIEVED BY PROCAINE INFILTRATION OF TWO TRIGGER AREAS IN LEFT PECTORAL MUSCLES 13 HOURS AFTER ONSET. RELIEF IMMEDIATE, COMPLETE AND PERMANENT.

INFLUENCE OF THERAPY ON PAIN

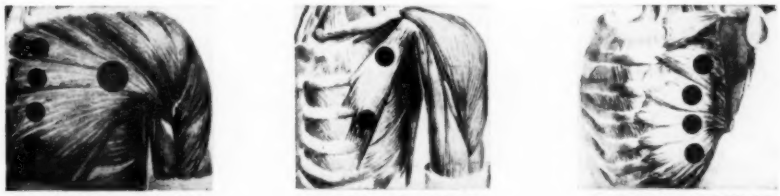


CHANGES OF ANTERIOR WALL INFARCTION





CLINICAL COURSE



PECTORALIS MAJOR — PECTORALIS MINOR — SERRATUS ANTERIOR

COMMON SITES OF SOMATIC TRIGGER AREAS WHICH REPRODUCE CARDIAC PAIN

EVIDENCE THAT PAIN WAS OF CARDIAC ORIGIN

SERIAL CHANGES IN ELECTROCARDIOGRAM
SIGNS OF CIRCULATORY COLLAPSE
SIGNS OF TISSUE NECROSIS

JFS

Department of Pharmacology
Cornell University Medical College

MYALGIA OF CHEST AND SHOULDER SIMULATING ACUTE MYOCARDIAL INFARCTION

H. H. 65 YEARS OLD. SUDDEN ONSET OF AGONIZING PRECORDIAL PAIN RADIATING TO LEFT ARM, WHILE WALKING. CONSTANT PAIN DURING 5 WEEKS PRIOR TO PROCAINE INFILTRATION OF TRIGGER AREAS IN LEFT POSTERIOR SCAPULAR AND INTERSCAPULAR MUSCLES.

COMPLETE IMMEDIATE RELIEF BY ONE SUCH TREATMENT. NO RECURRENCE IN SIX YEARS.

MAXIMUM EXTENT OF MOTION AT SHOULDER

JUST BEFORE INFILTRATION — 20 MINUTES AFTER INFILTRATION

EXTENSION 0° ABDUCTION 26° — CIRCUMDUCTION COMPLETE

EVIDENCE THAT PAIN WAS OF SOMATIC ORIGIN:

POSITIVE	NEGATIVE
MOTION LIMITED	NORMAL ELECTROCARDIOGRAM
MOTION PAINFUL	NORMAL TEMPERATURE AND BLOOD SEDIMENTATION RATE
PAIN CONSTANT, SEVERE AND CHRONIC	NORMAL CHEST X-RAY
REFERRED PAIN INDUCED BY PRESSURE ON TRIGGER AREAS	

Department of Pharmacology
Cornell University Medical College

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the office clinic

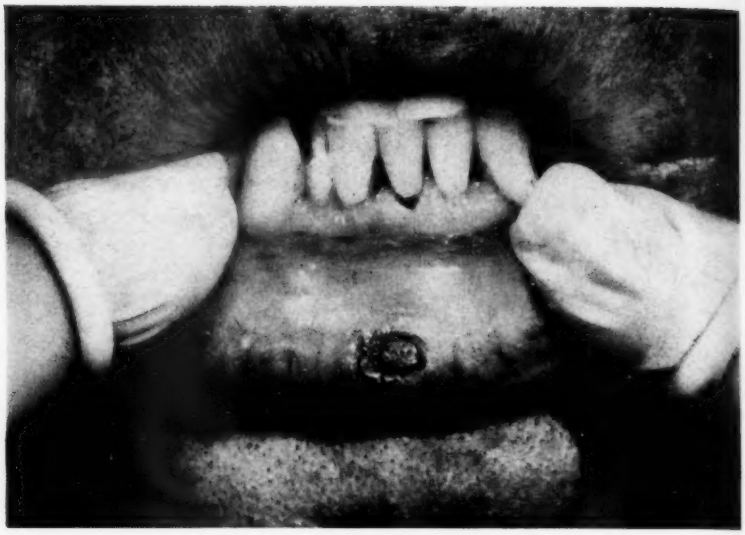
OCCASIONALLY, when a patient with a questionable lesion presents himself to his physician or dentist, symptomatic treatment only is administered. A mouth wash may be prescribed for a sore on the tongue. Or a lump may be regarded merely as a sign of some temporary inflammatory condition. Not infrequently, when biopsy is performed, these supposedly benign lesions are found to be malignant.

The pictures on the next two pages are of patients as they were seen by their physicians or dentists. The prognosis of cancer patients, such as those depicted here, depends almost entirely upon the actions of the first dentist or physician who examines them. If this initial diagnostician prescribes symptomatic treatment, and does not thoroughly examine the patient, he may miss the diagnosis. Only by employing adequate diagnostic measures — biopsy, palpation, laboratory studies, etc. — can the offices of the physician and of the dentist become effective cancer detection centers.

(Reproduced from THE CANCER BULLETIN)

1.

This lesion of the lip developed as a "little bruise", and was diagnosed by one physician as a "thickening of the skin". Biopsy by another physician revealed the lesion to be malignant. If there are no metastases and patient receives adequate surgical therapy, what is his prognosis?



Fortunately, prognosis in this case is good. In patients with lip cancer which has not metastasized, 65.1 per cent survive at least 5 years. Although this patient does not smoke, these lesions are often seen in pipe smokers.

2.

In November, 1950 this patient noted an ulcer on the gum and floor of his mouth. His dentist prescribed mouth washes; these failed to clear up the lesion. A biopsy performed in May, 1951 revealed squamous cell carcinoma. What would proper procedure have been in this case?

A biopsy should be performed on all persistent lesions of the oral cavity. Fortunately, in this particular patient, the disease was still localized; intraoral x-ray caused the tumor to disappear. Prognosis is good.

3.

This adenocarcinoma of the breast began as a painless lump. The growth is now large and extends into the axilla. There is also retraction of the nipple. Prognosis is poor. This woman probably could have been saved with earlier diagnosis. How might this have been accomplished?

If periodic examination of the breasts by a physician is impractical, the woman can aid the physician in detecting the early painless lumps that are suggestive of cancer by examining her own breasts every month.

4.

A sore on the tongue, and questionable nodes in the neck were this man's presenting symptoms. The patient was told to use mouth washes, but the sore did not heal. Three months later biopsy revealed a squamous cell carcinoma. This patient is a good candidate for what type of therapy?

Often, a combination of surgery and curie-therapy gives good results even in patients with lesions that have metastasized to the neck nodes. In treating patients with tongue cancer, each case requires separate evaluation.

A Summary of Cardiac Neoplasms

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CARDIAC neoplasms, though rather uncommon in occurrence, may be present in both males and females at any age. Metastatic tumors are more common than those of the primary type and benign tumors are more frequently found than are malignant primary growths.

In addition to the diagnostic criteria listed in the summary which follows, other aids to diagnosis include: Roentgenography, fluoroscopy, barium swallow, electrokymography, tomography, pneumopericardiography, angiocardiography, cytologic examination of pericardial fluid and roentgenkymograms, cardiac catheterization, and possibly, phonocardiography, ballistocardiography and various modifications of electrocardiography.

MALIGNANT TUMORS (sarcomas) are more frequent *on the right side* (auricle, interauricular septum or pericardium).

BENIGN TUMORS (myxomas) arise more frequently *in the left auricle.*

DIAGNOSIS

There may be no symptoms or signs and it may be impossible to reach a diagnosis. A tumor should be suspected when any of the following symptoms are present or when death occurs (8 and 10):

1. Unexplained or atypical, sudden, progressive, treatment-refractory congestive failure, especially in a young person.

2. Unexplained or atypical alteration in rate or rhythm and in the electrocardiogram, with tendency to rapid and sudden changes in the degree and type of aberration: heart block (Stokes-Adams syndrome), bundle branch block, nodal rhythm, auricular tachycardia, flutter or fibrillation, electrocardiographic findings suggestive of coronary occlusion or pericarditis.

3. Signs of atypical valvular disease, as mitral stenosis without adequate history of rheumatic fever; acquired pulmonic stenosis; tricuspid stenosis. Changes in findings with changes in position.

4. Suggestive subacute bacterial endocarditis without positive blood culture but with embolism.

5. Signs of unexplained obstruction to cardiac blood flow:

   a. Ball-valve action of tumor (often at mitral area), especially with position change and accompanied by severe dyspnea, cyanosis, unconsciousness, convulsions, etc.

   b. Tricuspid area obstruction with no known cardiac or pulmonic cause but with murmurs, right-sided failure.

   c. Superior vena caval obstruction with edema, cyanosis, venous engorgement of face and neck.

   d. Inferior vena caval obstruction (ascites, leg edema, hepatomegaly, collateral circulation).

   e. Cardiac tamponade by pericardial effusion or infiltration (falling blood and pulse pressures, tachycardia, pulsus paradoxus, dyspnea, engorged veins, hepatomegaly with friction rub, bloody pericardial fluid).

6. Roentgenographic findings of masses, contours, etc., not easily explicable.

7. Atypical anginal pains or suggestive coronary thrombosis.

8. Sudden death, especially without previous cardiac symptomatology.

9. Signs of malignancy elsewhere and changes in symptoms and signs as described in items 1 through 8.

10. Death from "noncardiac" cause in metastatic malignancy of unknown primary focus, with or without cardiac findings.

11. Mental retardation, adenoma sebaceum, congenital defects, convulsions with cardiac findings would suggest rhabdomyomatosis.

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Pediatrics

IN GENERAL PRACTICE

EFFECT OF THE ADRENOCORTICOTROPIC HORMONE (ACTH) ON NEPHROSIS IN CHILDHOOD

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The Jewish Hospital of Brooklyn

B. KRAMER

For almost a century the treatment of lipoid nephrosis has been a perplexing problem. From time to time various agents have been recommended because of a dramatic response in a small group of cases. Eventually most of these have fallen into disuse as a result of the discouragement that came with greater experience and more critical evaluation. Barness and his co-workers[1] have tabulated over 50 of these agents. During the last two decades two methods of treatment have received careful study and evaluation, namely, the effect of measles[2-4] and the use of repeated injections of low salt albumin.[5]

Diuresis in nephrosis occasionally has been observed to follow acute infections. Of the latter, measles has been found to be the most effective, not only producing diuresis with a fair degree of regularity, but also partially correcting the albuminuria, the hypoproteinemia and the lipemia of the disease. In a few instances permanent recovery has been observed. However, in the majority, after a brief interlude, the original condition recurs. Measles encephalitis, although uncommon, represents a definite hazard which gives rise to neurologic sequelae in over half of those affected and has approximately a 10 per cent mortality. Attenuation with gamma globulin negates the beneficial effect since only full blown measles is effective in promoting diuresis. In a disease such as lipoid nephrosis, where the possibility of recovery is approximately 60 to 75 per cent, the wisdom of utilizing such a potentially dangerous form of therapy is open to question.

Less hazardous and perhaps less effective is the use of repeated injections of low salt albumin. The rationale of this therapy is based on the marked albumin deficit in the blood plasma and the important role which albumin plays in the maintenance of normal serum

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oncotic pressure and hence upon the flow of fluid from the tissues to blood and from the blood into the urine. There is, no doubt, a close correlation between serum albumin concentration and edema. Where the former can be restored to a normal or nearly normal level, edema will disappear provided this situation can be maintained. The injection of large amounts of human serum albumin occasionally does raise the concentration of this blood component, although only temporarily. Even in those instances where an actual increase in concentration cannot be demonstrated, there may be an increase in circulating blood volume and diuresis may follow. Quantitative studies have accounted for almost all the injected albumin, in part as albumin excreted in the urine, plus a fraction utilized in the tissues and subsequently excreted as extra nitrogen, and a minimal amount remaining in the circulation. The occurrence of spontaneous diuresis in the absence of any change in the total serum protein level or in albumin content suggests that other factors are concerned in the mechanism of diuresis.

With the discovery of ACTH and cortisone, the attention of pediatricians has been focused on a hormonal form of therapy which in adequate dosage will provide a diuresis in about 60 per cent of children with nephrosis. Favorable results have been reported by Thorn,[6] Riley,[7] and Barnett and his co-workers.[8] It is the purpose of this paper to present our experiences with ACTH in the treatment of 12 children with the nephrotic syndrome. None of our patients had persistent hypertension, persistent azotemia or gross hematuria. These 12 patients received 19 courses of ACTH therapy, 13 of which resulted in a satisfactory diuresis.

METHODS

ACTH was administered intramuscularly every six hours in equally divided doses. In our early studies, the dosage was influenced by the eosinophil counts which were performed according to the method of Randolph.[9] If the initial dose of ACTH was not followed by more than a 50 per cent fall in the circulating eosinophils, the dosage was increased until such response was obtained. In the latter part of our study the patients were placed on a fixed dosage schedule without reference to the eosinophil counts. In our series, doses varying between 50 and 100 mg., and as much as 125 mg., were given daily. Although good results were sometimes obtained with 50 mg., 75 to 100 mg. per day appears to be the optimal dose. No apparent advantages were obtained when doses higher than 100 mg. were given. The dose was promptly decreased with the onset of diuresis.

Erythrocyte sedimentation rate was done by the Westergren method. Total and free cholesterol were determined colorimetrically by standard methods. Protein was determined by a micro-modification of the biuret method of Kingsley.[10] Albumin was determined by mixing 0.1 ml. of serum with 2.9 ml. of 24 per cent sodium sulfite and continuing with the biuret method.[11] Sodium and potassium were determined by the standard flame photometer according to the method of Natelson.[12] Calcium was determined by the method of Sobel and Sobel.[13] Inorganic phosphate was determined by the method of Sobel.[14] Urea was determined by the method of Sobel, Hirschman and Besman.[15] The Perkin-Elmer Tiselius Electrophoresis instrument was used for determining the electrophoretic patterns of the serum.

ILLUSTRATIVE CASES

Case 1—A 32 month old white girl was admitted to the hospital with a 12 week history of generalized edema. Two weeks after the onset of her illness, treatment with ACTH at another hospital was followed by diuresis. Three days after discharge, however, reaccumulation of fluid was noted and this persisted until her admission to The Jewish Hospital of Brooklyn two months later.

At the time of admission the patient had moderate generalized edema. She received a daily dose of 100 mg. of ACTH for 12 days. Her weight rose until the sixth day of therapy. At this time diuresis began and the lowest weight was reached six days after cessation of therapy. The erythrocyte sedimentation rate (ESR) dropped moderately before diuresis began; the cholesterol esters decreased with diuresis as did the total lipids; the urinary albumin dropped to zero, then remained at a trace with a decline in volume; the total protein did not

rise until maximum diuresis had been obtained but the albumin fraction rose early, even before treatment was discontinued. (Figure 1.)

Following discharge she was well for a month. Albuminuria then returned and there was a steady weight gain in the next four weeks. At this time she was again hospitalized and received a third course of ACTH with results similar to those obtained previously. One month after discharge, she was edema-free and clinically well.

Case 2—A 3 year old white boy was brought to the hospital with a 26 week history of progressive generalized edema. He was treated for 12 days with a total dosage of 735 mg. of ACTH. On therapy his weight rose gradually to reach a maximum on the ninth day of treatment, after which diuresis occurred, the lowest weight being reached three days after treatment was discontinued. ESR dropped three days before diuresis began and continued to fall after diuresis was established; the serum cholesterol dropped sharply, just prior to diuresis, to 40 per cent of its original level; the urinary albumin dropped from 4+ to a trace the day before diuresis began, after which the urine was albumin-free; the total protein rose after diuresis was well established although a rise in the albumin fraction was detected before diuresis. (Figure 2.)

Since discharge 10 months ago, the patient has had occasional mild periorbital edema and constant albuminuria (2 to 3+).

Case 3—A 5 year old white girl was admitted to the hospital with a six week history of edema. Physical examination on admission revealed mild periorbital and pretibial edema. The patient received 510 mg. of ACTH during a 10 day period. After an initial slight gain, the weight began to fall on the sixth day of therapy and reached a minimum three days after ACTH was discontinued. Although this child lost only three pounds, we consider this to be a favorable result since no clinical edema was present on discharge.

ESR seemed to be erratic (or very likely there was a laboratory error) but, following diuresis, returned to normal; the serum cholesterol dropped to 50 per cent of initial level with diuresis; the urinary albumin decreased about

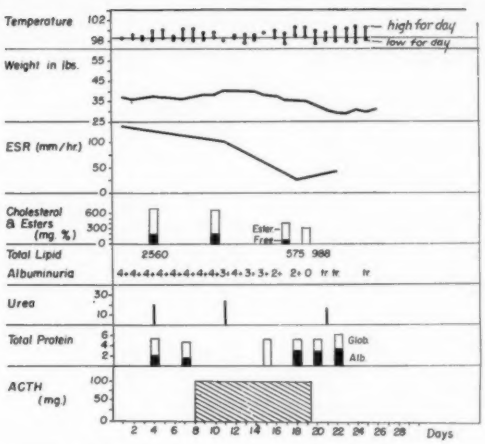

FIGURE 1 *(Case 1).*

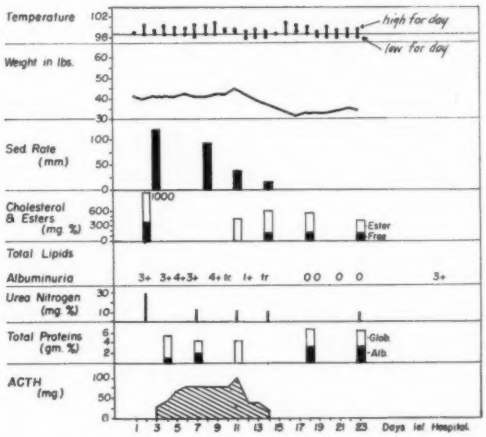

FIGURE 2 *(Case 2).*

six days before diuresis began; the total protein rose very slightly, but the albumin rose proportionately more. (Figure 3.)

In the eight months since discharge, this child has been clinically well except for mild periorbital edema associated with occasional upper respiratory infections.

Case 4—An 18 month old white girl was brought to the hospital with a one month history of generalized edema following an upper respiratory infection. Physical examination revealed no abnormalities other than moderate generalized edema. For three weeks the patient

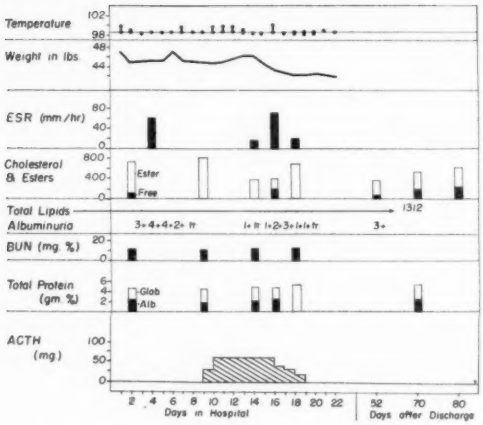

FIGURE 3 *(Case 3).*

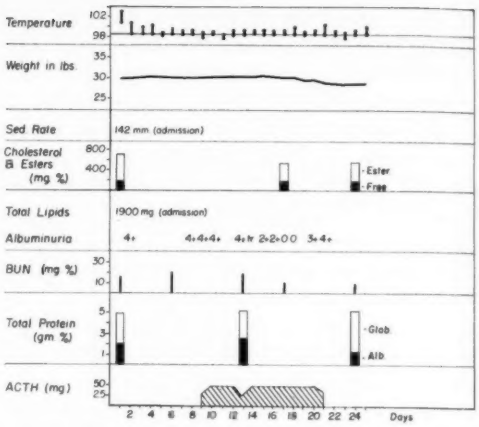

FIGURE 4 *(Case 4).*

was placed on a low sodium, acid ash diet with added ammonium chloride, with no response. Following this, a course of ACTH was begun. A total dosage of 537 mg. was given during a 13 day period (maximum daily dose, 50 mg.). Although this child lost 3 pounds, we consider this case to be a failure because of the persistence of clinical edema.

ESR was not determined; there was a 20 per cent fall in serum cholesterol; there was a transient fall in the urinary albumin, but this reverted to pretreatment levels before ACTH was discontinued; there was no significant change in the total serum protein although the albumin fraction showed a transient rise while on therapy. (Figure 4.)

This child was subsequently treated at another hospital with larger doses of ACTH which resulted in a diuresis. Since that time (10 months ago) she has had several exacerbations and spontaneous remissions.

Case 5—A 4½ year old white boy was admitted to the hospital with a 12 week history of progressive edema following an upper respiratory infection. At the time of admission physical examination revealed marked generalized edema and ascites. The patient was treated with 675 mg. of ACTH during an eight day period. After a gradual increase in the weight, diuresis began on the sixth day of therapy. Four days after treatment was discontinued the patient weighed 32 pounds, as compared with a pretreatment weight of 46 pounds. This patient's course was complicated by an episode of abdominal pain, tenderness and rebound tenderness which developed on the seventh day of therapy. He was considered to have peritonitis and placed on antibiotics. The following day ACTH was discontinued and within two days the condition had subsided completely.

ESR fell coincident with diuresis; the total cholesterol remained essentially unchanged; the urine became negative for protein when diuresis was well established; the elevated blood urea nitrogen fell to normal; the total protein remained essentially the same, but there was an appreciable rise in the albumin fraction. (Figure 5.)

Two months after discharge, the patient was well except for mild periorbital edema.

Case 6—A 3 year old white boy was brought to the hospital with a one year history of progressive edema interrupted by several spontaneous remissions. Moderate generalized edema and ascites were present on admission. The child was treated with 720 mg. of ACTH for a 13 day period. There was a 2 pound weight loss but no appreciable change in clinical edema and therefore we consider this case a failure.

ESR did not change appreciably; the total cholesterol remained at the high initial levels; the total serum protein and the serum albumin remained unaltered; there was a transient decrease in the proteinuria. (Figure 6.)

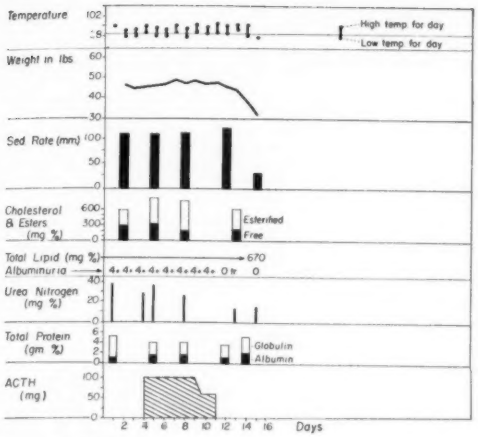

FIGURE 5 *(Case 5).*

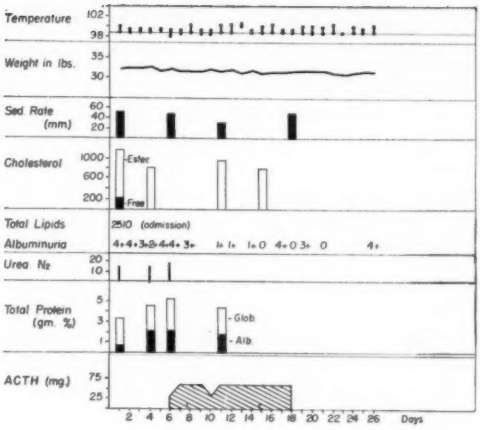

FIGURE 6 *(Case 6).*

In the year since discharge there have been several remissions and exacerbations usually associated with upper respiratory infections.

Case 7—A 2 year old white girl was brought to the hospital with a one month history of progressive edema. On admission marked edema and ascites were noted. She received 1000 mg. of ACTH during a 12 day period. Diuresis began on the tenth day and four days after ACTH was discontinued the patient had lost 11 pounds. The patient's course was complicated by a fall in serum potassium to 10 mg. per cent on the eleventh day of therapy. This was accompanied by confirmatory changes in the electrocardiogram, but without symptoms of hypokalemia. With oral administration of potassium chloride the serum potassium level quickly reverted to normal.

ESR fell to normal at the time of diuresis; the total serum cholesterol and total serum lipids also fell at the time of diuresis but did not reach normal levels; the urine became negative for protein when diuresis was established; there was little change in the total serum protein but the serum albumin rose appreciably. (Figure 7.)

The patient has remained clinically well in the two months since discharge.

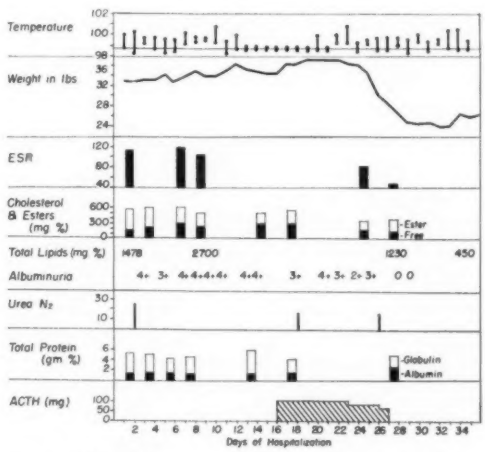

FIGURE 7 *(Case 7).*

RESULTS

In our 12 patients, 7 of whom were boys, 19 courses of ACTH were administered. There were 13 satisfactory diureses. The other 6 courses either were total failures or were followed by a small weight loss without disappearance of clinical edema. One patient received 5 courses, 4 of which were total failures. In 2 other patients there was a small weight loss but clinical edema persisted. One of the latter subsequently received larger doses of ACTH at another hospital and satisfactory diuresis ensued. The other has never been re-treated and is the only patient in whom a diuresis was not obtained at any time with ACTH. In the 9 remaining patients, 11 courses were given, all of which were successful.

One patient made a complete recovery and has remained well for one year with normal chemical values in the blood and urine. Seven patients who have been followed for one to nine months are now clinically well except for occasional minimal edema. The laboratory values in these patients are improved but still moderately abnormal. Two patients who have been followed for one year have had complete clinical as well as chemical relapses. The child who received 5 courses of therapy with only one diuresis following the third course was later treated successfully with measles and is clinically well five months later. In the patient in whom diuresis was never obtained, the course of the disease has been unaltered. (Table 1.)

TABLE 1

FOLLOW-UP STUDY OF 12 NEPHROTIC PATIENTS TREATED WITH ACTH

	PATIENTS IN WHOM DIURESIS WAS NOT OBTAINED *(Total, 1)*	PATIENTS IN WHOM DIURESIS WAS OBTAINED ONE OR MORE TIMES *(Total, 11)*
Complete recovery		1
Partial recovery*		7
Clinical relapse**		3
Completely refractory	1	

*Occasional minimal edema with improved but abnormal chemical findings.

**One patient subsequently treated with measles.

COMPLICATIONS

The complications we have seen with ACTH therapy are for the most part those reported in the literature. Hypertension (diastolic pressure of 100 mm. of mercury or more) was seen in 4 cases. One patient developed a systolic blood pressure of 170 and a diastolic blood pressure of 110 and it was necessary to discontinue therapy for a short period. Euphoria and increased appetite were noted in a majority of the patients. None of our cases developed glycosuria. Two patients developed hypokalemia. Both responded favorably to oral administration of potassium chloride. There were two severe infections in our series. One child developed pneumonia on the twelfth day of ACTH therapy; the second developed peritonitis on the tenth day. In both instances antibiotics were administered and ACTH discontinued. Both patients made uneventful recoveries in a few days. Neither of these patients received prophylactic antibiotic therapy. It is of interest to note that no severe infections were encountered in the 6 patients who did receive prophylactic antibiotics. In the light of our experience and that of other investigators, prophylaxis of this type would seem to be indicated.

LABORATORY DATA

During the treatment of our patients, repeated determinations of the following laboratory data were obtained: serum sodium, serum potassium, serum chloride, carbon dioxide-combining power, serum calcium, serum inorganic phosphorus, serum total and free cholesterol, serum total protein and albumin-globulin ratio, urinary albumin, and erythrocyte sedimentation rate. Total serum lipids were obtained in four patients. (Table 2.)

Except for the two instances of hypokalemia mentioned before, no significant changes were noted in the serum sodium, potassium, chloride, or carbon dioxide-combining power.

There was a slight but definite increase in the serum calcium and a similar decline in the serum inorganic phosphorus. The average pretreatment serum calcium and inorganic phosphorus values were 8.3 and 5.2 mg. per cent respectively. The corresponding post-treatment values were 9.2 and 4.2 mg. per cent respectively. A rise in serum calcium and fall in inorganic phosphorus were not obtained in only 2 instances, both of which represented total failures of ACTH therapy. The probable explanation for the increase in the serum calcium is the corresponding rise in the serum albumin level, while the decrease in the serum inorganic phosphorus may be referable to the interference with phosphate resorption by the renal tubules during diuresis.

In our cases the initial values for serum total cholesterol ranged from 450 to 1200 mg. per cent with an average of 776 mg. per cent. During all but two courses of treatment the cholesterol tended to return toward normal. In only two instances was a normal value obtained. The average post-treatment total cholesterol value was 533 mg. per cent. Initially the percentage of free cholesterol averaged 31 per cent while the corresponding final value was 28 per cent.

TABLE 2

CHEMICAL CHANGES IN NEPHROTIC PATIENTS TREATED WITH ACTH

	AVERAGE VALUES	
	Before ACTH Therapy	*After ACTH Therapy*
Total protein (gm.)	4.9	5.6
Albumin (gm.)	1.7	3.1
Globulin (gm.)	3.2	2.5
Total cholesterol (mg.)	776	533
Per cent free cholesterol	31	28
Calcium (mg.)	8.3	9.2
Phosphorus (mg.)	5.2	4.2
Total lipids (mg.)	2,212	840

In normal adults Jerome Conn[16] has observed a drop in both total and free cholesterol in the plasma after ACTH, the free cholesterol dropping less than the total, thus giving a relative increase in free cholesterol. He attributes the greater decrease of esterified cholesterol to the fact that it is the precursor of the adrenal steroid hormones. Our results indicate that in the nephrotic patient ACTH in most instances depresses the free and the esterified cholesterol approximately equally. The significance of these observations is not yet apparent.

The total serum protein rose from a mean of 4.9 gm. per cent prior to therapy to 5.6 gm. per cent after therapy. Before treatment was started the albumin fraction was never higher than 2.4 gm. per cent, with a mean of 1.7 gm. per cent. However, after therapy, the serum levels of albumin increased markedly to a mean of 3.1 gm. per cent. There was a slight fall in the serum globulin from a mean of 3.2 gm. per cent to 2.5 gm. per cent. That the rise in the total protein represented the difference between the considerable increase in the albumin fraction and a small decrease in the globulin fraction was corroborated by studies of the electrophoretic pattern. In the unsuccessfully treated cases there were no significant changes in blood proteins.

In the four cases in which it was determined, the average serum total lipid fell from a mean of 2,212 mg. per cent to 840 mg. per cent.

Prior to therapy, urinary albumin ranged from 3 to 4+ in all cases. In every case the urinary albumin diminished while on therapy, in all but three instances reaching zero or a faint trace.

In all but one of the successful cases a drop in the erythrocyte sedimentation rate preceded diuresis. In 6 instances it fell to normal values. This is the only laboratory value that returned to normal with any degree of frequency.

The electrophoretic pattern in the serum of patients with lipoid nephrosis is distinctive.[17] It consists of a very low albumin spike, a small gamma globulin peak, and a large, irregular combined alpha two and beta component. With diuresis following ACTH therapy there was a marked increase in the albumin spike and a resolution of the confused alpha two and the beta component into separate peaks.[18] No change was found in the gamma globulin component.

DISCUSSION

Diuresis appeared at a variable time during the course of ACTH therapy. In the majority of cases the diuresis began while the patient was receiving ACTH, but in a few instances it did not begin until ACTH was discontinued. Usually one or more of the following changes preceded diuresis: a drop in the ESR, a decrease in the total serum cholesterol, a rise in the serum albumin, or a sharp decrease in proteinuria. None of these changes, however, was found to be an invariable indication that diuresis was imminent.

Just why diuresis occurs is not clear. ACTH is known to produce at least a temporary retention of sodium and chloride[19] and to increase plasma volume.[8] Thorn[6] postulates that the diuresis which occurs after ACTH is discontinued is due to failure to reabsorb sodium, chloride and water as a result of relative adrenal insufficiency. The observations of Barnett[20] indicate that ACTH produces an improvement in the function of the nephrotic kidney as manifested by an increase in glomerular filtration rate, maximum tubular capacity and renal blood flow. In cirrhosis of the liver as well as in a variety of other diseases characterized by a low serum albumin, ACTH has induced an increase in the latter presumably by improving liver synthesis of serum protein.[21] Lawson's observation[22] on the effect of ACTH in decreasing glomerular permeability to protein may serve to explain the decrease in albuminuria that occurs and this may partially account for the increase in serum protein.

The relative importance of each of these factors in the promotion of diuresis is not known. It is possible that none of these is the primary factor.

It is interesting to note that ACTH acts to suppress all the known clinical and chemical abnormalities of nephrosis. The shift of the plasma protein pattern, the fall in the serum lipids, and the decrease in urinary albumin and ESR are all in the direction of normality, but only in the case of the sedimentation rate is there a return to absolute normality with any degree of frequency. Soon after the drug is discontinued there is a tendency for these values to revert to pretreatment levels, although in many cases partial improvement persists for some time.

Spontaneous diuresis may occur without any of the changes in the blood that follow the administration of ACTH. Diuresis with ACTH does not occur unless such changes are observed. It does not appear that these changes are the result of the diuresis, for in many cases the changes begin before diuresis. Since all the chemical abnormalities tend to revert toward normality and all at approximately the same time, one must suppose that in some manner ACTH counteracts the effects of some noxious agent responsible for the manifestation of nephrosis without actually destroying this agent. The effect is similar to that which one observes in rheumatic fever, namely, a suppression of the clinical phenomena of the disease, and, as with the latter, it still remains to be determined whether the total duration of the disease is actually shortened and recovery hastened by this treatment.

While many interesting observations have been made, the pathogenesis of nephrosis and the mechanism of diuresis, whether spontaneous or artificially induced, still remain unsolved problems. It is hoped that further studies of the effect of ACTH will help clarify these problems.

CONCLUSIONS

ACTH is definitely not a cure for lipoid nephrosis in childhood.

Diuresis with complete disappearance of clinical edema results in more than 50 per cent of patients.

Changes in certain blood components have been described, but except for the ESR, these seldom return to normal.

Relapses occur in a majority of cases after from a few days to a few months.

Clinical recovery may be enjoyed for a variable period of time, but blood studies will reveal characteristic abnormalities.

Further observations, perhaps with larger doses and longer duration of treatment, may yield better results.

The treatment gives the patient a respite from the discomfort of gross edema with minimal danger of unpleasant complications.

The prophylactic use of antibiotics and oral potassium is recommended.

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GENERAL PRACTICE *Review*

For general practitioners, as well as specialists, this department offers the latest, proved methods of treatment of conditions encountered in an average practice. It is not, of course, intended to present these discussions as the only acceptable therapeutic procedures to be used, but rather to offer simple regimens and recommendations based on the extensive experience of the physicians who prepared these summaries.

BACILLARY DYSENTERY

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Bacillary dysentery is an acute infection of the bowel caused by bacteria of the *Shigella* group. *S. paradysenteriae* is the infecting organism in the majority of cases; *S. dysenteriae, S. sonnei, S. schmitz* and *S. ambigua* are other members of this group. Only *S. dysenteriae* produces an exotoxin. The infection is transmitted by patients, human carriers and flies. The portal of entry is through the gastrointestinal tract following the ingestion of contaminated food or water. Bacillary dysentery appears in epidemic, endemic or sporadic form, wherever and whenever sanitation is poor and personal hygiene is faulty.

The incubation period ranges from one to seven days and usually is less than four days. The onset of symptoms frequently is sudden, with fever, nausea and vomiting, abdominal cramps, tenesmus and diarrhea; as many as 20 to 40 watery, bloody stools may be passed daily. The excessive loss of body water and the dehydration may lead to severe prostration.

The chief physical findings are fever, evidence of dehydration, and tenderness over the colon. Sigmoidoscopic examination reveals an intensely hyperemic mucosa with edema, friability, bleeding and mucopurulent exudate; the appearance is not unlike that of nonspecific ulcerative colitis. The severity of the disease varies from the asymptomatic carrier form to a fulminating, occasionally fatal illness. Symptoms may subside after several days or persist for three to six weeks. Relapses are common.

Various complications have been described, such as arthritis, urinary infections, ischiorectal abscess and fistula-in-ano. The disease clinically may be indistinguishable from typhoid, paratyphoid fever, *Salmonella* infections or acute fulminating ulcerative colitis.

The diagnosis of bacillary dysentery depends on the isolation and identification of the infecting organism. Unless it is done immediately, it may be difficult to culture the organism. Microscopic examination of the feces reveals a large

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number of polymorphonuclear cells, erythrocytes and macrophages. The changes in the intestinal mucosa vary from hyperemia in the milder cases to inflammation and ulceration of the entire bowel wall in more severely ill patients; perforation is rare. The diseased colon in bacillary dysentery usually heals completely; permanent scarring may result in the rare instances of deep ulceration. The prognosis is good. Fatalities may occur especially in the very young or the aged; with prompt, effective treatment the mortality rate is less than 1 per cent.

TREATMENT

Treatment consists of general supportive care and the use of sulfonamides and antibiotics. Complete bed rest is desirable during the acute phase. The patient should be kept isolated and sanitary measures instituted as for any enteric infection. An adequate fluid intake is desirable. Severe diarrhea and the excessive loss of fluids may result in electrolyte depletion and necessitate the intravenous injection of isotonic sodium chloride in 5 per cent dextrose; sufficient amounts should be given to insure a daily urinary output of 1000 to 1500 cc. The administration of plasma may be required in the presence of severe dehydration and peripheral vascular collapse.

During the acute phase the intake of food is limited to small amounts of liquids such as tea, bouillon and barley water; the diet is increased gradually and a bland, low residue diet is maintained until the infection has subsided completely. Abdominal pain and discomfort may be relieved by the application of heat to the abdomen and by sedatives and antispasmodics; the combination of phenobarbital, 0.03 gm., and extract of belladonna, 0.0075 gm., in tablet form is a convenient preparation. Atropine sulfate, 0.0005 or 0.001 gm. hypodermically, also is helpful. The abdominal pain may be so severe as to require codeine or morphine sulfate temporarily. Catharsis with castor oil or sodium sulfate would seem unnecessary in view of the severe diarrhea.

The sulfonamides inhibit in vitro the growth of all types of *Shigella*. Their clinical efficacy has been difficult to evaluate because of the self-limited course of the disease. However, the usefulness of sulfonamides such as sulfaguanidine, SULFASUXIDINE®, sulfadiazine and sulfathiazole in bacillary dysentery has been emphasized repeatedly in the literature. The readily absorbed sulfadiazine is preferred because it reaches the site of infection more effectively. The initial dose is 3 or 4 gm. by mouth, followed by 1 gm. every four to six hours. Therapy should be continued for 7 to 10 days. The criterion of cure should be three consecutive negative stool cultures. Persistently positive bacterial cultures usually indicate the presence of a sulfonamide-resistant strain. The administration of one of the newer antibiotics—chloramphenicol, aureomycin or terramycin—is then advisable. The usual dose is 0.25 or 0.5 gm. every six hours; the administration of 2 gm. initially, followed by 1 gm. every 12 hours, for two doses may suffice even in severe cases. It should be noted that these antibiotics may themselves cause abdominal distress and diarrhea. Favorable results in the treatment of bacillary dysentery have been reported also with neomycin (0.5 gm. orally four times daily) and with polymyxin B orally in doses of 15 to 20 mg. per kilogram of body weight daily for 10 days.

Bacteriophage therapy is ineffective. Antidysenteric serum is of no practical value, with the possible exception of infection with *S. dysenteriae*. Antiserum administered promptly in such cases is useful in neutralizing the neurotropic toxin. Polyvalent antidysentery sera are prescribed occasionally in patients with severe bacillary dysentery but their value is not established.

The eradication of the organism in the chronic, symptomless carrier may be difficult, especially when the organisms develop resistance to sulfonamides. Excellent results recently have been reported with bacitracin given orally in doses ranging from 1,000,000 units daily for eight days to 4,000,000 units daily for 30 days; uniformly good results are described during follow-up periods of from three months to three years.

The prevention of bacillary dysentery depends on adequate sanitation, including the proper disposal of feces and sewage, adequate fly control, protection of food and water from fecal contamination, hand-washing by food handlers

after defecation, pasteurization of milk and the avoidance of uncooked fruits or vegetables in regions where sanitation is poor. Carriers should be identified promptly and treated until the bacteriologic cultures are consistently negative.

No method of immunization has proved satisfactory as yet. Vaccines probably confer some degree of protection but immunity is neither absolute nor lasting; future developments in this field may provide more effective methods of protection against bacillary dysentery.

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AURICULAR FIBRILLATION:

Mechanism, Significance and Therapy

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Auricular fibrillation has long been a fascinating subject for investigation and conjecture in the field of cardiology. When Sir Thomas Lewis[1] propounded the theory of "circus movement" as the pathologic physiologic mechanism causing this arrhythmia, it was felt by most cardiologists that the basic cause for its occurrence had been established and that the end of the road had been reached as far as understanding this arrhythmia was concerned. After more than 40 years the theory was firmly established and almost universally accepted. A few had both good and poor arguments against Sir Thomas' reasoning, but none could advance their arguments with sufficient force to arouse widespread doubts about this seemingly established theory.

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With the forward surge in the study of cardiac physiology that has taken place in the past decade, we not only have acquired a different concept of the nature and mechanism of auricular fibrillation, but also have arrived at a more comprehensive attitude toward its significance and its treatment.

It now seems that Prinzmetal[2] has established beyond doubt the fact that auricular fibrillation is caused by multiple stimuli arising in the auricles and spreading throughout the auricles according to the conductive ability of the auricular musculature. That this results in a "pot-boiling" or "delirium" of auricular activity is probably still agreed. That there is consequent inefficient circulation of blood through the auricles with stasis in the auricular appendages, and frequent formation of thrombi in these appendages, is also generally accepted.

It should be stated, and probably emphasized, that all cases which in the past have been called auricular fibrillation probably are not. It seems that, with the recent increase in the use of chest leads, roughly 20 per cent or more of regularly occurring waves of electrical potential, usually associated with auricular activity, are seen in the chest leads, especially in leads V_1 and V_2. While we have not conducted simultaneous standard lead-chest lead recordings, it is our opinion that a large percentage of cases diagnosed as auricular fibrillation in the standard leads really represent auricular flutter. Good proof of this point is the rather constant observation that, as the chest lead positions are traversed from position V_1 to position V_6, the higher voltage and well defined P waves go through a transition to waves of lower voltage and ill defined "f" waves. We cannot explain with certainty why these waves appear to change in this manner. It is our opinion that the pathway of the excitation waves over the auricles does not change, but that, as the exploring electrode moves farther away from the auricles, only the potentials of higher voltage are recorded. This is due either to the distance or to the angle of the electrical axis in relation to the frontal plane. These higher voltage potentials may be variables which, after a certain distance from the auricles or because of a more perpendicular angle from the frontal plane, have recorded only the peaks or other portions of auricular activity. As a result, the irregular, ill defined "f" waves are recorded from a distance and the well defined, rapidly recurring P waves of auricular flutter are recorded from electrodes placed in closer proximity to the source of potential representing the auricular activity.

It is a common observation that in many instances the well defined P waves seen in leads V_1, V_2 and V_3 also reveal potential variations which, at times, vary cyclically and, at times, vary quite irregularly. It must be admitted that this may not apply to all cases of auricular fibrillation and auricular flutter, because frequent instances of flutter occur in which there are well defined P waves in all or nearly all the usual routine leads. This could be due to certain degrees of auricular dilatation and/or to hypertrophy. The converse is also true, since there are many instances in which only the "f" waves of auricular fibrillation are recorded in all the usual routine leads. An interesting study could be made on this point by observing the recording of auricular electrical activity by the use of esophageal leads. This should be done with the electrodes applied at the site of greatest auricular electrical activity as well as during the passage of the electrode beyond (caudad) the auricles and during the withdrawal of the electrode.

It must be mentioned that in a small percentage of instances of auricular flutter the well defined P waves are recorded in all the limb leads, both standard and unipolar. Also, an extremely large percentage of cases of auricular fibrillation are recorded as ill defined "f" waves in all leads. It seems, however, that when "f" waves are recorded in the standard and unipolar limb leads, and in the chest leads farthest away from the auricles, e.g., V_3 through V_6 or higher, we must conclude that there is no significant change in the electrical activity within the auricles during the time required to record the tracing in the succeeding chest positions. Instead, we would think that the relatively low potential of auricular activity is not accurately recorded at the distance or angle from which these leads are recorded. If this reasoning is correct, it would seem that we should more

often diagnose the arrhythmia as auricular flutter, rather than auricular fibrillation, when the chest leads V_{1-2}, and sometimes V_3, show well defined P waves, and when all the other limb and chest leads show "f" waves.

SIGNIFICANCE OF AURICULAR FIBRILLATION

Auricular fibrillation can occur as a transitory arrhythmia, in the nature of a paroxysmal tachycardia, without demonstrable associated heart disease or other known cause. It can be due to extracardiac factors as well as to certain well known types of heart disease. It is observed early in arteriosclerotic heart disease and usually late in all other forms of heart disease.

EXTRACARDIAC ETIOLOGY

The probable extracardiac etiology that exists in such cases may include toxic or infectious factors, e.g., too much coffee; excessive smoking or drinking of alcoholic beverages in the presence or absence of excessive fatigue; overwork and/or lack of rest, with or without exposure in inclement, especially cold, weather. Excessive fatigue from overwork and/or lack of rest alone may be the only demonstrable etiology. Other toxic etiology includes excessive thyroid administration, excessive digitalis administration and, presumably and theoretically, many other drugs. Hypoxia during anesthesia may produce auricular fibrillation, with or without associated heart disease. We have found application of a body cast which restricts respiration to be associated with the onset of auricular fibrillation in a 55 year old man with evidence of moderate chronic arteriosclerotic heart disease. It is also possible for trauma to cause auricular fibrillation, with and without attendant serious permanent damage to the auricular or ventricular myocardium.

ETIOLOGY ASSOCIATED WITH HEART DISEASE

1. Hyperthyroidism. Treatment usually starts with 10 drops of Lugol's solution three times a day and, if necessary, 50 to 100 mg. of propyl thiouracil three or four times a day. Sedation and elimination of tension may also be hepful.

2 and 3. In the absence of hyperthyroidism, the development of auricular fibrillation most commonly is associated with moderately advanced or far advanced rheumatic heart disease and usually with involvement of the mitral valve. Another commonly associated disease is early arteriosclerotic heart disease.

4. Many instances of acute cardiac infarction of the ventricular musculatures are ushered in with an associated auricular fibrillation. In these cases the associated angina is often difficult to elicit and, still more often, difficult to evaluate. While the clinical picture usually suffices to establish a diagnosis of infarction, it is not at all unusual to find it necessary to make serial electrocardiographic studies over a period of from several days to two weeks in order to secure adequate electrocardiographic confirmation of the clinical impression. It is not known whether infarction of the auricles occurs simultaneously in such cases. Nor has it been common to see auricular fibrillation in those cases of infarction of the auricular myocardium which have come to our attention.

5. The advanced stage of almost any form of heart disease is often associated with auricular fibrillation. This is true of pure forms such as hypertensive cardiovascular disease, congenital heart disease, heart disease of unknown etiology and heart disease of any combined etiology including pulmonary disease, heart disease associated with right ventricular strain as well as left ventricular strain, thoracic deformity or bacterial endocarditis. The latter may be more often associated with pre-existing disease when auricular fibrillation is present.

TREATMENT OF AURICULAR FIBRILLATION

Consideration of the etiologic basis—Successful treatment includes, first, treatment of the underlying disease so that the enumerated etiology provides a guide to the appropriate therapy. This should be kept in mind for every patient. Not too long ago (and it may be that the custom still prevails throughout a large section of our country) it was felt that, in most instances when auricular fibrillation occurred in association with far advanced heart disease, it was better for the comfort of the patient to permit chronic fibrillation to continue, rather than to attempt to convert the arrhythmia back

into a regular sinus rhythm. This was especially true when repeated remissions were associated with disagreeable symptoms. It is our impression that it is best to try to convert auricular fibrillation to a normal rhythm, whenever possible, on the basis that a regular sinus rhythm is a more efficient rhythm. This is probably true in all instances of recent occurrence.

When fibrillation becomes refractory to treatment, and further efforts to convert the arrhythmia prove unavailing, corrective therapy probably should be stopped. With this attitude, attempts to convert auricular fibrillation would be stopped on the basis of actual failure of management, rather than because of the discomfort to the patient caused by going into and out of auricular fibrillation. Definite measures should, of course, be taken in order to try to prevent recurrences of auricular fibrillation.

Loosening extensive body casts or tight bandages of the thorax in appropriate cases is just as important as the use of digitalis or quinidine. Possibly related toxic or infectious agents, such as coffee, tobacco, alcohol, overactivity or lack of rest should be eliminated. Some authors stress the need for reducing tension and emotional stress.

DRUG THERAPY

Digitalis—A digitalis preparation is probably the drug of choice in the absence of toxic or infectious etiology, and it often may be necessary in the presence of infectious etiology. This would be especially true in the presence of a "fast fibrillation," e.g., when the ventricular rate is very rapid—more than 100. The use of rapid digitalization measures is permissible, but intravenous administration almost never is warranted. A 165 pound patient could be given 1.2 mg. of digitoxin, or 25 gr. of the powdered leaf of digitalis, during the first 24 hours. This medication could be administered as 0.3 mg. of the digitoxin or 6 gr. of the powdered digitalis leaf four times a day. Such a dose would be given in the presence of a very rapid ventricular rate or in the presence of associated ventricular failure.

In the absence of an extremely rapid ventricular rate or marked ventricular failure, smaller amounts of digitalis are advisable in order to avoid the untoward effects of digitalis intoxication. We employ the dose of 0.2 mg. of digitoxin three times a day until the heart rate is slowed to between 70 and 80, and then reduce the dosage according to the requirements of the patient and to the ease with which the rate is slowed. If the rate slows quickly, the dose would be reduced to 0.2 mg. digitoxin twice a day on the second or third day, to once a day on the third or fourth day and 0.1 mg. thereafter. In older patients and in small or slender individuals, the dose might be reduced to 0.1 mg. digitoxin every alternate or third day.

Similarly, the digitalis leaf would be given in 1½ or 3 gr. doses three times a day for one or two days and then gradually reduced to 1½ gr. twice a day, after the rate has slowed to below 80, and then to once a day, or once every two or three days, according to the patient's tolerance and weight. There is a possible growing tendency to return to the use of the digitalis leaf rather than digitoxin because of greater ease in stabilizing the dosage.

It is almost never necessary to resort to intravenous digitalis therapy for auricular fibrillation, even when the ventricular rate is quite rapid.

Quinidine—In the absence of evidence of decompensation, it is advisable first to try quinidine sulfate in doses regulated according to the ventricular rate. For rapid ventricular rates over 150, it is advisable to begin with 6 gr. of quinidine sulfate four times a day. If the ventricular rate is under 100, we also use 6 gr. for the first oral dose, followed by 3 gr. four times a day. In patients weighing 120 pounds or less, 3 gr. will be given three times a day after the first day.

When patients without manifestations of decompensation or hyperthyroidism fail to respond to 3 or 6 gr. of quinidine sulfate four times a day, the dose may be increased until manifestations of cinchonism develop. These are usually manifested by tinnitus, flushing, diarrhea or nausea. Quinidine has been used in doses as high as 450 gr. per day for some cases of paroxysmal tachycardia without harmful effect. Care should, however, be exercised and close observation maintained when large doses are employed.

Recently, quinidine has become available in ampule form for intramuscular injection. In the presence of rapid ventricular rates, this prepara-

tion could be used in an attempt at rapid conversion of auricular fibrillation. The single ampule, e.g., quinidine sulfate, 3 gr., can be given intramuscularly every one or two hours up to six times in 24 hours. This could be supplemented by the usual oral doses which can be continued every two hours until normal sinus rhythm is restored or until signs of cinchonism develop.

Combined digitalis and quinidine therapy—It is no longer felt that the combined use of digitalis and quinidine produces a high incidence of pulmonary infarction. This combination can be used in every instance when the single drug does not convert the auricular fibrillation into sinus rhythm. The combination is usually used in the presence of decompensation or some form of long-standing heart disease which is of advanced degree.

LONG-TERM DOSAGE AND DURATION OF THERAPY

In simple attacks of paroxysmal auricular fibrillation, and in the absence of decompensation, it is probably advisable to continue therapy for two or three weeks after normal rhythm has been restored. A gradual reduction of the dosage may be instituted, such as reducing the quinidine sulfate to 3 gr. twice a day after the third week of normal rhythm, while in the fourth week it would be reduced to once a day. In this manner the patient could use the total amount prescribed.

Similarly, the dosages of digitoxin and digitalis could be halved at the end of the third week of normal rhythm and the total amount of the drug prescribed utilized in this manner.

For recurrent attacks of paroxysmal auricular fibrillation, it is best to use the minimal dosage of whichever drug is used. It usually is an individual matter for each patient and has to be worked out on an individual basis. Some patients, especially those who have chronic arteriosclerotic heart disease, may require as much as 3 gr. four times a day, whereas others may require less, e.g., twice a day, once a day, every other day or twice a week. Some patients prefer to wait until a spell recurs and, in such instances, it is probably best to recommend 6 gr. doses at four hour intervals until the rhythm becomes normal and then to use 3 gr. three or four times a day for two or three weeks thereafter.

In the presence of cardiac decompensation and advanced forms of heart disease, the maintenance of a regular sinus rhythm is more difficult and requires digitalis, with or without quinidine, for long periods of time and often on a permanent basis. It is difficult to evaluate the benefit derived from quinidine in such patients, especially in the presence of chronic fibrillation. In such cases, attempts should be made to determine how much aid is given by each drug used and to discontinue quinidine, for example, when it gives no help in reducing the degree of irregularity of the ventricles. Digitalis preparations usually are the drugs of choice in slowing the ventricular rate.

In the presence of slow ventricular rates of 60 to 70 or the low 80's, quinidine probably is the drug of choice and should be used in conservative amounts. In the absence of other demonstrable causes, the older age of these patients and the chronic arteriosclerotic heart disease may constitute the basis for the slow ventricular rates. There probably is no universal agreement on the treatment of such patients when they do not respond to quinidine or to digitalis preparations. PRONESTYL®, procaine amide hydrochloride, is known to be of no value for treating this arrhythmia.

In keeping with our new approach to geriatric medicine, it may be advisable to try aminophylline, THEOCALCIN®, papaverine or other coronary dilators and, in the event of failure, to continue our endeavor to reverse the arteriosclerotic process. The latter would include a study of lipid or cholesterol metabolism and, possibly, the newer approaches to a consideration of connective tissue metabolism and nervous tissue metabolism, as well as all possible combinations which, separately or together, could comprise the underlying cause of changes in the auricular musculature which result in increased irritability of the muscle cell, which, in turn, causes the chaotic electrical and mechanical activity of auricular fibrillation.

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Editorials

MAY 1952

POSTGRADUATE MEDICINE

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COMMENTS ON CHOLESTEROL

We have an active research program in our department* on the subject of nutrition in relation to arteriosclerosis. This program involves attempts to produce in animals a type of arterial lesion which will serve as an experimental counterpart to the human disease. This will allow an investigation of the role of nutrition in arteriosclerosis. We are attempting to extend and confirm the important work of Dr. Gofman on the inter-relation of cholesterol, lipoproteins and atherosclerosis.[1] Our conclusions to date are more conservative than those of Dr. Gofman.

There are a great number of different lipoproteins in the blood and since most of these contain cholesterol, all of the various fractions must eventually be studied. Whereas attention was first centered on the S_f 10-20 group, a recent paper from Dr. Gofman's laboratory now suggests that those of higher S_f values may also be related to atherosclerosis.[2] Keys suggests that the evidence to date on the S_f 10-20 class of lipoproteins does not show better correlation with atherosclerosis than does the measurement of cholesterol.[3]

Many technical problems remain also. As yet, we have little information on the accuracy of the determination of lipoproteins, variability from day to day in the same subjects, and what causes the variability. Recent data collected in our laboratory show that these variations are not inconsiderable and it is important to know what causes them. Finally, it should be pointed out that when exhaustive statistical analysis is required to show the correlation between two variables, such as lipoprotein level and atherosclerosis, it usually means that there are many other variables whose effects are unknown or uncontrolled and that such correlations are of relatively *little value* for predictive purposes. The fact that one may be able to show statistically significant correlation between two variables may have relatively little to do with cause and effect. The wide range in the data presented to date does not lead one to place much reliance on the lipoprotein determination for predicting the likelihood of the development or presence of atherosclerosis.

It may seem logical for many individuals that *if*—and we emphasize the if—one can show a relation between high serum cholesterol or lipoprotein values and atherosclerosis, then low cholesterol diets are automatically desirable. A consideration of what we now know will not support this logic. It was once thought that if you wanted to fatten a hog you should feed a high fat diet.

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This editorial is a digest of remarks presented by the senior author at the Symposium on Overweight, Nutrition and Health at the Clinical Session of the American Medical Association, Los Angeles (December) 1951.

It has been known for a long time that the fat in a hog is largely made from carbohydrate and that the fat of the diet is not directly deposited in the body. The situation with regard to cholesterol appears similar. Cholesterol is made in the body from smaller fragments, including acetic acid, which in turn arise from sugar, fat and protein. A consideration of this fact alone makes it obvious that low cholesterol diets may have no effect on the cholesterol content of the body.

Further, evidence indicates that low cholesterol diets do not decrease the cholesterol content of the serum. Keys was unable to show a relation between dietary and blood cholesterol in normal men over a wide intake of cholesterol.[4]

In some species, notably the rabbit and chicken, atherosclerosis may be produced by feeding large amounts of cholesterol. Yet in the dog, the same kind of diet is ineffective unless one interferes with the thyroid function; in other species, a relation of dietary cholesterol to atherosclerosis has not been found in spite of much study. Just where the human species lies in this array of responses is unknown.

One can decrease serum cholesterol by feeding fat-free diets, at least in some species. This is certainly not a practical approach and it should be noted that the vegetable fats, while free of cholesterol, have no advantages over animal fats in their influence upon serum cholesterol. Finally, the work of Gould[5] and Taylor suggests that the synthesis of body cholesterol may be so regulated by unknown mechanisms that less is made when the diet contains cholesterol and more when the diet is low in cholesterol. If this should be confirmed, it immediately becomes apparent that we must look further than dietary cholesterol if we wish to influence cholesterol content of the body.

There seems to be a prevalent idea that cholesterol is a wholly undesirable substance. It should be pointed out that it is an essential constituent of all animal tissues and undoubtedly plays an important role in the normal function of all cells.

To eliminate cholesterol from the diet means the elimination of animal foods from the diet—meats, milk, eggs, etc. These are the protective foods which nutritionists have clearly shown are essential for an adequate diet, unless very careful dietary control is managed with vitamin, mineral and protein supplements. The proposition that low cholesterol diets be used as a preventive for the development of atherosclerosis would mean that animal foods be omitted from our diets. This is equivalent to the negation of practically all that nutrition science has taught us in the past. Such a course might well be disastrous. Anyone inclined toward this teaching should seriously consider the very slight evidence upon which it is based and be mindful of the greater damage which he might do.

It is always possible that there may be metabolic errors in the atherosclerotic patient such that low cholesterol diets may be beneficial to him. What then? Under such conditions the services of a well trained dietitian will be required to assure that the diet is adequate. Nutrition science has advanced sufficiently that such diets are possible. We only wish to emphasize the dangers of such diets when not adequately devised. The use of therapeutic diets is an entirely different matter from the recommendation of diets for widespread use for the possible prevention of disease. The latter implies changes in the general dietary pattern for everyone.

It may be concluded, therefore, that while nutrition undoubtedly plays an important role in the etiology of atherosclerosis, there is insufficient evidence as yet to define this role with any degree of exactness. There certainly is no evidence that meatless, milkless, eggless diets should be recommended as desirable to the general public.

D. M. HEGSTED, G. V. MANN AND F. J. STARE

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ON THE READING OF BOOKS

When civilization in Mesopotamia became so complicated it could no longer be transmitted from one generation to another by word of mouth, our forebears learned to write and, through necessity, they made books. Some of these books reported what was known of medicine in that day. Many of our botanical and medical words can be traced to Mesopotamia.

With rare exceptions, everything worth knowing among civilized people has been recorded in books. Chaucer said the new learning of his day came out of old books. Paraphrasing the words of Francis Bacon, critical reading maketh the full man, ready in conference and exact in writing.

As repositories of knowledge, books have met many needs and the accumulated store has served well all succeeding generations. Their utilitarian scope is not limited by intellectual and cultural interests. Not long ago the *Saturday Review of Literature* carried a picture of one of our ancestors standing in the mouth of his cave with a heavy clay tablet poised above his head. His woman, with "daggers in her eyes," cowering before him on the dirt floor, exclaimed, "You throw another book at me and I'll leave home." Beethoven once declared that his maid was much more amenable after he had thrown six books at her head. Solomon said, "Of the making of books there is no end." Yet as missiles for matrimonial discipline he must have found them useful.

Francis Adams—who translated Hippocrates into English—while a country doctor on horseback, saved a gamekeeper's life by placing a copy of Horace over the femoral artery, using his handkerchief as a tourniquet and the turn of a spurtle (porridge) stick for sufficient pressure to control bleeding. The availability of his Horace is understandable when it is recalled that often this great scholar was seen reading on horseback with his pockets stuffed full of the classics. And finally we should not forget the lifesaving virtue of the bulletproof Bible in the soldier's jacket. Perhaps no less useful was the stack of books that boosted the suicide over the balustrade of the Brooklyn Bridge.

To the physician who has developed the habit of reading, books are as essential as air and light. They mate with his moods, they inform his mind, interpret his needs and become his friends. On the cultural side of medicine, books unlock the gates of the past, reveal medical traditions, recount scientific achievements, supply incentives, arouse ambitions, and inspire action.

Osler said, "To study the phenomena of disease without books is to sail an uncharted sea." He might have added, to drift idly in unproductive waters is to remain ignorant of opportunity and to miss the satisfaction of accomplishment. Well chosen medical books faithfully perused may fill psychologic sails for exciting journeys in research or rewarding diagnostic and therapeutic adventures accompanied by fascinating psychosomatic connotations and experiences.

No longer are books close cloistered. Even in remote places they can be made accessible. In this day of intellectual democracy ignorance is fatal. Yet the freedom to write, to print, to publish, and to read may become a bane. With a surfeit of books at hand it is easy to become careless and superficial. In the profession of medicine nothing can be worse than an intellectual parasite drawing sustenance from the tree of medical science.

Physicians who do not read are obviously wanting in culture and deficient in professional skills—those who only skim the printed page are mere medical chameleons; those who drink deep and taste the author's lifeblood are genuinely cultured and competent.

LEWIS J. MOORMAN

AN EXPERT (?) REMARKS ON THE NEGRO HEALTH PROBLEM

MR. Oscar Ewing, Federal Security Administrator, spoke recently before the Manhattan Central Medical Society, an organization of Negro physicians in New York City. According to the *New York Times,* Mr. Ewing said that "the most important factor bearing on the problem of Negro health is that 'the average Negro has less than a fair chance for health because he is not a lucrative patient.' "

Here is a quote from Maxcy, "Preventive Medicine and Hygiene":

"The Negro mortality appears to be declining somewhat more rapidly than the white mortality."

Here are some quotes from the report of the Commission on Hospital Care:

"Because of their low social and economic status and because of prevailing racial attitudes, Negroes have not had cultural and educational advantages equal to those of white people . . . The literacy of the people is reflected in their use of and demand for modern health services. It may be expected that as the education of the Negro people is advanced, they will demand more medical and hospital care."

"Negro death rates in the United States . . . are 60 per cent higher than those of white people . . . Homicidal deaths are 11 times more prevalent among Negroes than whites, but suicide is only one-third as prevalent. Deaths from syphilis are six times and from tuberculosis almost four times more prevalent among Negroes. Pneumonia and nephritis are twice as prevalent among Negroes. Many factors contribute to these differences."

"Negroes in low income groups do not participate to any great extent in the nonprofit plans. This is due partly to the economic status and partly to race prejudice."

Now, Mr. Ewing, aren't you ashamed of your statement which is unwarranted, untrue and in itself an incitement to race prejudice and race discord? You also said, Mr. Ewing, that "the only way to improve the health and life expectancy of the Negro people is through a program of national health insurance." If that is so, Mr. Ewing, why did Mr. Truman appoint the Magnuson commission?

MORRIS FISHBEIN

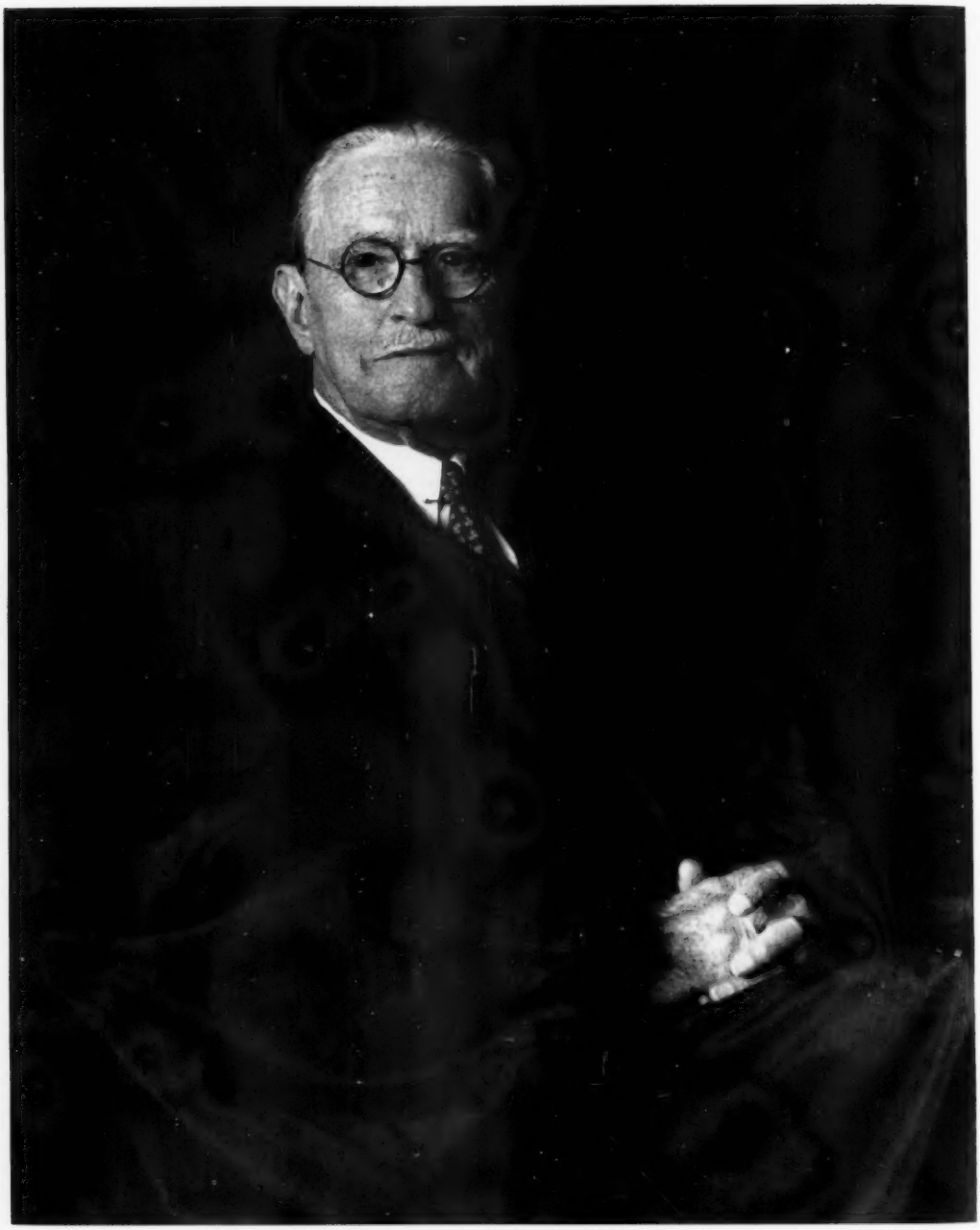
HEALTH NEEDS AROUND THE WORLD

CARE has recently organized a committee to aid in provision of health and medical facilities around the world. The committee is headed by Dr. Morris Fishbein, contributing editor of *Postgraduate Medicine,* and includes:

Dr. Louis H. Bauer, secretary-general, World Medical Association; Mr. Elmer H. Bobst, president, Warner-Hudnut Company; Dr. Perrin H. Long, professor of medicine, Long Island University; Mr. Basil O'Connor, president, National Foundation for Infantile Paralysis; Dr. Milton Winternitz, director, Division of Medical Science, National Research Council, and Mr. James J. Kerrigan, president, Merck and Co., Inc.

Some of the immediate problems that have been placed before the committee are the provision of artificial respirators for Japan, layettes for Israel, maternity outfits for India and drugs in many places throughout the world.

Poliomyelitis appeared first in Japan following the arrival of American troops and is now showing a tendency to increase year after year. From April 1950 to March 1951 there were 3,212 reported cases with 810 deaths. In many instances the infection was of the bulbar type. Unfortunately there have been only two respirators available in Japan and those were borrowed from a station hospital of the Allied Forces. At present only one such respirator remains and the need for additional respirators is acute. CARE proposes to establish artificial respirator centers in various places in the Far East where they can be made available in case of epidemics. The medical profession is, of course, greatly interested in such projects and further information will be supplied from time to time.



TIMOTHY LEARY, M.D.

MEN OF *Medicine*

Pathologist, Professor, Public Servant

THE imagination of the public, industriously stimulated by thrillers in every medium from the Broadway stage success to ten cent pulps on the newsstands, has developed certain standards of picturesqueness for all of the cast of characters. There are gun-totin' sheriffs, deceptively friendly prosecuting attorneys, and hard-boiled medical examiners so inured to violence and horror that the most fiendish crime elicits hardly more than a raised eyebrow. So when it is announced that Timothy Leary was for 42 years Medical Examiner for Suffolk County—the southern district, which includes Boston—there is a sigh of anticipatory relish for the gruesome tale to be unfolded.

But Dr. Timothy Leary is a man who has filled many roles and performed many tasks. In his long and useful life the more sensational murders have faded into the background where they still glow with lurid color, but dwindle into insignificance beside the importance of his contributions to our knowledge about alcoholism and coronary disease. And his attention was directed to those two subjects because they are the great killers of the destitute and the drifters whose dead bodies passed through his hands. Of 44,400 deaths certified in his years of service a great number were due to coronaries; of 15,000 autopsies he performed, 3000 were on coronaries. To a man possessed of Dr. Leary's stern sense of duty and sensitive conscience, the lesson was clear. It was his responsibility to do something about it, and he did. The first logical step was to find out *why*.

He is inclined to minimize the importance of the work he did on alcoholism, pointing out that without substantial grants of money and an adequate staff little can be done in so broad a field. Yale University's studies of alcoholism certainly deserve commendation, he offers. But men who know Leary's early work—some of them collaborators and later independent investigators who have continued the studies of alcohol poisoning—are quick to praise him. "He was the first pathologist in America to take alcoholism seriously, to study the organs and tissues of people who died of it. Every day of his life was devoted to pathology: teaching, practice, research. His has been a long life of useful work well done, and we're all lucky he's been spared to write down what he found out."

With a whimsically appreciative smile that spreads from his lips to his fine brown eyes, Dr. Leary may accept the encomium, even adding a few observations about the extraordinary variations in the ways beer or gin affects the human liver: the one enlarges it, the other dries it up. But it's obvious that his spirited fight for the proper labelling of whiskies has been relegated to the past, along with his extensive collection of whiskey bottles that had brought their possessors crime, violence and death.

The doctor's current and continuing enthusiasm is the study of crystalline ester cholesterol and its relation to various conditions, e.g., atherosclerosis and adult cortical renal tumors. He is the author of many publications on these subjects, and though confined to his home with a chronic back ailment associated with osteoporosis, he keeps up his study and writing. Moreover he is eager for publicity, not for himself—he has a New Englander's ingrained distaste for the sensational or the conspicuous—but "for the protection of the victims of coronary disease from the chemist's suggestion that the low fat, low cholesterol diets be abolished in the treatment of that disease," and he'll see to it that the publicity is forthcoming. A phar-

maceutical house is now printing 10,000 copies of his paper, "The genesis of coronary sclerosis," for distribution to general practitioners. The doctor is pleased, but in his own words, "continues to wear a 7⅛ hat," and pushes indomitably forward the unceasing campaign of disseminating life-saving knowledge.

As a matter of fact Timothy Leary exemplifies so many of the fine qualities that are habitually labelled "typically New England" that it's a bit startling to learn that his progenitors had nothing to do with the Mayflower or any other craft Massachusetts-bound. Instead his grandfather, one John Leary, in 1820 walked from St. Johns, New Brunswick, to Boston, settling in Waltham where he got a job as chain man of the crew surveying for the Fitchburg Railway. Timothy's father was chairman of the board of selectmen of Waltham, and was also appointed postmaster. In that capacity he introduced the carrier system, using veterans and sending young Tim out with the horse and carriage to deliver any left-over parcels or late arrivals. He was an enterprising and scrupulously conscientious citizen who, when he ran for mayor was defeated and saddened because his opponent attacked his Catholicism, hammering at the electorate the slogan, "Remember! The mayor will also be chairman of the school board!" Perhaps Dr. Timothy Leary is well content to have established his own family home in Jamaica Plain on a quiet, middle-class street that leads from a busy shopping center and car line down to the shore of Jamaica Pond.

The pioneering urge of the Learys was still strong in Timothy's blood, and in '98 he answered the Surgeon General's call for trained medical men in Puerto Rico. He was a mere youngster, having graduated from Harvard in '95, the class that also included Elliott Joslin and Harvey Cushing. Next year he was licensed to practice and served as house surgeon at the Free Hospital for Women. In Puerto Rico life was at once regimented and challenging. On the hills above the little port of Ponce was a military hospital, windows open to the balmy air, high-studded rooms crowded with soldiers because, as the young newcomer from Boston was told, "everyone had malaria." Leary, already inclined toward pathology, made careful examinations of blood samples, equally careful autopsies. Many of them revealed acute, three-day typhoid. The military officer admitted he'd been wrong; he and the young doctor continued to get on well—a tribute to the Leary personality that combines warmth with respect for discipline and hard work. He was amused and appalled at the men of the Wisconsin regiment who wore toothbrushes in their campaign hats as a salute to the antiseptic age, but nonchalantly washed clothes above where men drew water for drinking.

Leary was first executive, then commanding officer. Gradually, the $100,000 worth of tents and equipment went back to the Quartermaster's Corps and he was relieved of that responsibility. More to his taste was the part he played in the vaccination of 800,000 people in Puerto Rico, a very early project, completely controlled, and successfully carried out in the face of ignorance and opposition that expressed itself through one editor who claimed that the army men went about infecting people and making them lose their arms. He was forced to retract, and the doctors carried on, producing their own vaccine, soothing a frightened populace, and eventually stamping out smallpox on the island. Young Leary was fortunate in working under an able and congenial director, Major Azel Ames of Quincy, author of the "Log of the Mayflower." Their job received official commendation and they started home.

At Santiago, Cuba, the transport was met with reports of an epidemic of yellow fever. Timothy Leary volunteered to remain and take the place of the resident pathologist who had succumbed to the fever. With his bags he was dumped on a wharf in the dark where he stood listening to his companions' farewells as the ship drew away. They promised to send back a few cubic feet of earth from God's country (New England, of course) so he could have a proper grave! The young man trudged up the unfamiliar street, sought out General Leonard Wood, and went promptly to work as a member of the Yellow Fever Board and as pathologist for the hospital. It was up to him to pick out the yellow fever patients and send them to the isolation hospital. He still remembers that the disease picked out blondes and boozers, while

he himself, dark, aquiline, abstemious, was terrifically bothered by fleas! Aristides Agramonte was in charge; from him too the newcomer learned much. Before the epidemic was over, five of seven nonimmune medical officers contracted the fever; two died. The emergency ended, Leary returned home, and in 1901 was made Professor of Pathology at Tufts.

But 1952 provides a neatly appropriate footnote to a young man's experience in a dangerous plague spot. On April 26 of this year the House Officers' Association of the Boston City Hospital presented to Dr. Timothy Leary, for distinction and outstanding service, the Leonard Wood Medal. The General himself was one of Leary's famous predecessors at Boston City Hospital, and the award is made annually to a former staff member whose achievements warrant it. Seldom has it been more appropriately conferred, or the recipient more deserving. Honoring Dr. Leary threatens to become a habit at City Hospital. He has also received the Charles V. Chapin gold medal, and delivered the first Chapin Lecture to the Rhode Island Medical Society.

Back in Boston young Timothy Leary found both work and welcome awaiting him at Tufts. He had already served an apprenticeship at that school in the department of bacteriology and pathology and he fell to work with a will, holding steady the helm and steering the course embarked upon by his predecessor, Dr. Henry W. Dudley, who had been the first head of the department. In the early years of the century Tufts had barely a toehold in medical education, being completely overshadowed by Harvard with its graduating lists of superior persons. But even then Leary and one or two colleagues saw that New England sorely needed well trained country and town practitioners. They never lost sight of that objective. Even today Dr. Leary writes: ". . . There are certain fundamental matters that should be a part of the knowledge of every practitioner of medicine. The present paper ('The genesis of coronary sclerosis') deals with the steps in the evolution of one of the most important human diseases—and more specifically with its development in the most critical site of its manifestations." And he is proud of present day innovations at Tufts, e.g., the one month refresher course seminar series conducted for doctors from Maine and New Hampshire at no cost to them.

Perhaps needless to say Tufts is also proud of Dr. Leary and, on his resignation in 1929 after 32 years of service, the Tufts medical alumni honored him with the biggest medical dinner ever given in Boston. With extraordinary insight President Cousens likened Leary to the chief of a wild German tribe conquered by Roman legions, Christianized by force and total immersion. But as the baptizing centurion pushed him beneath the water, the intrepid leader held his sword arm, blade in hand, aloft and ready. Leary was never caught unprepared!

His personal motto, borrowed from William Harvey, and the one he never ceased to urge on his students, was less spectacular but extraordinarily productive: *Dii omnia laboribus vendunt.* He has always been a perfectionist, drove himself and others hard, expecting much from them, and getting it. Louis Phaneuf recollects the strenuous days he spent studying for his summa at Tufts and working in Leary's laboratory as well. The doctor surveyed him critically and observed: "Now, young man, if you'll work hard you might possibly amount to something." Young Louis Eusebe Phaneuf kept his nose relentlessly to the grindstone. Twenty-five years later, tense, burdened, successful, he met Dr. Leary on the hospital steps and the older man was moved to compassion.

"You know, Louis, you should let up a little and not work so hard."

Dr. Phaneuf bowed. "Perhaps I will now. I've been awaiting that word from you for a quarter of a century!"

All Dr. Leary's students respected and stood more than a little in awe of him. They are agreed that he was a lecturer of the Virchow school, formal—not to say formidable—precise, unapproachable. It was understood among the students that if you managed to pass Leary's courses you'd unmistakably demonstrated your fitness for a degree. It was his duty and practice relentlessly to comb out those without minds. And he combed 'em out—vigorously! He never forgot that to doctors is entrusted the ultimate responsibility of dealing with human lives.

White-haired Dr. William Edward Browne

has vivid recollections of those lectures. "You never realized they were lectures—they weren't, they were masterpieces. He'd walk in, punctual to the split second, erect, dignified, impeccably dressed in frock coat and striped trousers, a pointer and sheaf of notes in his hand. He'd stack them on the table and never glance at them again. Always he'd begin, 'Today, we will discuss such and such. It is a continuation of our discussion of yesterday . . .' And the period would go on while he defined the aim of his remarks, stated its important attributes, and pursued it through numerous descriptive entanglements. At the end of 55 minutes he carefully integrated all he'd talked of, picked up his notes, turned on his heel and went out.

"We'd been sitting there with our adrenals working overtime, so scared our palms were sweating, but all the time we knew we were learning from a great man's mind. After one of his lectures we felt we'd increased our capital stock of knowledge. We were solemnly assured that if we got by the tumor part of his course, we'd have a pretty good chance of squeezing through. He defined numerous types of tumors of the breast and discussed each, wonderfully well. I have the notes today which I made back in 1910, and they're better for reference than some of the modern pathology textbooks."

Yet a man as severe as that in what he demanded of himself and others was capable of stopping everything to help a deserving person who was struggling futilely to reach a goal. "Oh, he was the old-style, formal professor all right, but he was generous too," recounts another student. "Why one time he gave me a whole brain!"

During most of his years at Tufts Dr. Leary was also Medical Examiner for Suffolk County (southern district), an office to which he was appointed by six governors of Massachusetts, the first of them Governor Curtis Guild in 1910. It was he who had occasion to congratulate Leary on his friends, for after a faculty controversy about the candidate to be recommended for the post, Leary emerged with 16 votes, his opponent with one!

The system of medical examiners whose duty it is to inquire into all violent or potentially violent deaths was initiated in Massachusetts in 1877 when the abuse of the appointment as coroner had become so staggering that there were 43 coroners in Suffolk County alone. Many other states now use the system which is endorsed by both bar associations and medical societies. The unswerving integrity and conscientious devotion of such men as Timothy Leary have done much to make the office respected and important.

Always a believer in the tutorial system of education, Dr. Leary instructed groups of 7 to 10 medical students in the autopsy room at Boston City Hospital. He insisted on certain standards of cleanliness and decorum at the dissecting table as well as in the operating room. He never lost his idealistic views of the medical profession—or of humanity. At times he'd say: "I'd have you students bear in mind that you're privileged to learn something from the tissues of this individual now dead. You owe, therefore, a debt of gratitude to the dead who are now helping you to help others to live better."

Awards and honors interested him little. His constant endeavor was, by means of eye, scalpel, microscope, to try to fathom what went on in the chemical and physical laboratories of living that resulted in such changes that death became inevitable. Detecting the common denominators of blood vessel disease and heart disease sent him hurrying from the autopsy room to the records department to get a history of the individual's life. What did he eat, drink? What were his habits, his excesses? Finally he unravelled successfully what many believe to be dogma concerning the harmful effects of cholesterol in persons unable to metabolize it, and the resultant changes in walls of blood vessels culminating in early death.

As one would suppose, he was a stickler in matters of detail in ferreting out the cause of death, yet he never allowed his work to leave behind it a scar of terror or anguish in the hearts of those close to the one on whom an autopsy was necessary. He was composed but never callous when a mother had to be told that her son had been found dead, or a young wife asked to identify a broken and mangled body.

At first thought it is difficult to reconcile the neat, calm, gently austere Dr. Leary with the

violence and notoriety which his job as medical examiner necessarily involved. To say he doesn't like sensationalism is understating the case—he abhors and detests it. Yet for many years he worked closely with the police—often finding he even had to think for them—in bringing law and order to the chaotic world of drug peddlers, abortionists, drunkards and murderers. The key doubtless lies in that overlooked word, order. Dr. Leary's own integrity expressed itself in precision and exactness; moreover his mind was quick, trained, perceptive. He could indeed get to the heart of the matter and lay it bare as with a knife. The Boston police reporters recognized that quality and paid tribute to it in presenting Dr. Leary with the black Harvard rocker in his living room.

Tales of those adventure-packed days are many. They range from the case of the Charleston Navy Yard machinist who brought home a huge egg of cyanide to poison his second, unwanted wife but was acquitted by a sentimental jury unable to resist the ostentatious grief of a row of the prisoner's pious relatives, to the famous case of the handsome divinity student and the simple choir singer. That chronicle, as packed with human interest and pressure of circumstance as Dreiser's "An American Tragedy," had all Boston agog for weeks.

Dr. Leary, pressed to choose a "favorite murder case," wouldn't nominate either. His choice falls on The Stabbing in Franklin Park because it was "a distinctly medical murder," and therefore his own case, from the first garbled account to the inescapable solution—and conviction of the murderer.

"It all started one Sunday evening on Morton Street when a young man, dishevelled, wounded, bloody, stumbled from his car pleading only half coherently for help. He drove onto Morton Street from a road in Franklin Park closed to automobile traffic, where, he maintained, a murderous assault had taken place. Once the wound on the back of his neck had been dressed at a neighboring hospital, he led police back to the deserted road in Franklin Park where on the grass lay a young woman, dead.

"As he told it, he and the young woman, whom he had known for some time and to whom he was very much attached, had been driving together in his car. Earlier, when he'd made the engagement with her, they'd thought of going to a movie, but not seeing one they thought they'd enjoy, as they drove around, they headed out toward the winding wooded roads of Franklin Park. They were both in an emotional, not to say overwrought, state. The young man had been drafted into the army and was due to leave next day. He had been pleading with the young woman, an attractive divorcee with a child, to marry him before he left for training camp. She had refused him, continued to refuse him while declaring she was fond of him, willing to be friendly. During their discussion he slowed down the car, thinking they'd park and talk further. They had reached a road bounding Franklin Park on the south.

"Just at that moment a man leaped from the shrubbery, flung open the rear door of the car and, crouching in the back seat, pressed a pistol against the young man's head. He then ordered him to drive to Morton Street and thence to the road closed to automobiles. There they stopped. The young man was conscious of a series of blows or shots as his companion was wounded; then he himself was slashed in the back of the neck. Groggy and wavering he opened the car door, slipped out from under the wheel, and staggered down the road. He found no one to help him but, partially revived by the night air, went back to the car. The girl crawled out of the front seat on her side of the car to join him, ran for a few steps and then collapsed. He carried her for a short distance toward an arc light down the road, but had to drag her with her heels scraping the ground. He laid her on the grass, went back to the car and sought help. He was sure that an inmate of the neighboring Boston State Hospital (for mental disease) had murdered her and he was frantic with grief.

"At the mortuary, inspection of the nude body made plain that this was indeed a murder. There were 10 stab wounds so located as to indicate without shadow of doubt that the young woman's assailant had been standing by the left front door of the car, not crouching in the back seat. The story the wounds told began with a slash across her left upper arm as she lifted it to protect her face. As she strained away, her attacker caught the thin blue silk coat she was wearing and tried to stab her to the heart, but inflicted only two wounds in the armpit. The fabric of the coat was not pierced. As she continued to pull away from him, he stabbed seven more

Dr. Leary is shown being sworn into office as Medical Examiner of Suffolk County (Massachusetts) by Governor Maurice Tobin in 1946.

times across the right and left chest and back. The car revealed that the girl had bled to death with her head on the driver's seat, which, covered with a wool blanket, was soaked with blood. That seat had been unoccupied during the stabbing. Furthermore, it was evident that she died in the car because, as he dragged the body out under the wheel, her knees collapsed on the ground, tearing her stockings. The skin beneath was deeply scraped and torn but showed no bleeding, for she was already dead at that time.

"The killer was the young man who had driven the car, not a mythical marauder. Eventually he was found guilty of murder in the second degree, a verdict based on the clearly detailed story told by the medical evidence, the wounds and the blood in the car. An appeal to the Supreme Court failed to upset the decision.

"The man was an unstable type, enraged with jealousy at leaving her. If he couldn't have her, no one else should. But what convicted him was purely medical evidence. Observed and interpreted by a medically trained mind, it told what had happened more objectively and exactly than any eye witness. That's why I call it a 'medical murder.' "

It could never be said of Timothy Leary, as is so often lightly remarked of eminent men, that if you don't know him off the job, on his own time, you don't know the real man at all. Dr. Leary's life has been very much of a piece: public service, teaching, research and publication of the results have been closely woven with his family life and his personal interests to produce a symmetrical and orderly pattern. It is difficult to unravel certain bright threads and arbitrarily label them "hobbies," yet they reveal much about the man. None of them really fall under that stilted heading; indeed, chuckles his old friend James Ballard, of the Boston Medical Library, "The man's interest in Benjamin Church amounts to an obsession. Leary's the greatest defender that old fraud ever had!"

"Fraud? Traitor? I should say not," asseverates the indignant Dr. Leary, "why Benjamin Church was the first Surgeon General of the American Army, an able physician and a poet to boot. I've always been interested in the early history of this country—been a member of the Colonial Society of Massachusetts—and I knew how lucky I was when Church's medical manuscript notebooks came into my hands. They consist largely of notes on his lectures in England. He married there, but later returned here and had a 'pleasaunce' in Raynham. There were some Puritan whispers about orgies there, but there's no reasonable ground for the man's being called a traitor. He was an extremely able and interesting person. One of these days I'm going to write a book about him and prove it!"

It's a scholarly, gentle hobby capable of ramifications in further historical research, and always good for a spirited argument with fellow antiquarians—in whom Boston abounds.

His second hobby has these many years been embodied in a fine institution, the Forsythe Dental Infirmary for Children, and Dr. Leary thinks of it rather as a project that filled his mind and his leisure time during some of his most active years.

"The genesis of the whole thing was odd and interesting—so was how I came to be so closely

identified with it. James Bennett Forsythe was the patient of a colleague of mine, a dentist and Tufts professor named Dr. Ervin Johnson. Forsythe, along with his brothers, came to this country as penniless immigrants, but they built up a great fortune. Woven hose it was. Ordinary fibrous hose was one thing, but Forsythe combined rubber and the usual fiber so his hose would hold water—or any other liquid for that matter. And one day he said to Dr. Johnson that he'd set aside a half million dollars for a charity, some charity, he didn't know what! Johnson was delighted; he came to me and we talked it over, but meanwhile old James died suddenly leaving no will. Fortunately the family had known of his wish and they were agreeable to the idea of a dental infirmary for children. Indeed they pushed it, but they asked me to be a trustee, and that project was really my baby. We wanted it to be a modern surgical building; we kept asepsis and mouth hygiene in front of us every time we examined a blueprint or approved a contract. We planned a unique waiting room for children; had a competition of young artists to do the decoration. And to face the tiled stairwell going up to the second floor we put in Paul Revere's ride—all in specially made tile. There's the Roxbury Giant too . . . and sometime take a look at the bronze doors; their design was my idea."

Foursquare, stately, and dignified, the Forsythe Dental Infirmary stands today a worthy neighbor of Boston's famous Art Museum, and still a modern surgical building more than 30 years after its completion. Dr. Leary worked there on the side; Percy Howe, the first man to do practical work with vitamins and their relation to the human dental system, worked there. Today students from all over the world are trained there, and each year the top student of the graduating class in every American dental school is given an opportunity to come there to study. Fluorine treatments during the growth period, unheard of in 1912, are considered important now, but whatever the requirements Forsythe's facilities can handle them. And the great carved bronze doors above the granite steps commemorate a noble concept. One shows the figure of a brooding mother, "giver of life and love"; the other a symbolic figure of the

United States Hospital, Ponce, Puerto Rico, 1898.

Dr. Leary while a student at Tufts Medical College.

commonweal which bestows "health and learning." James Forsythe and his generous notions fell into good hands.

There is a postscript to the story that is even more pertinent to Dr. Leary than to the donor. When the Learys were starting on a long planned, eagerly anticipated trip to Europe, Thomas Forsythe, genial and open-handed, pressed into Dr. Leary's hand a $100 bill, urging him to use it for a gay "extra." There was no refusing; the doctor worried and pondered, but on his return he brought for the Forsythe Infirmary an exquisite Della Robbia bambino of glass mosaic from the island of Murano in Venice. Dr. Leary's integrity and taste are both without question.

Art has always appealed deeply to the doctor; he longed to own something fine, something authentic. Neither reproductions nor the second-rate satisfied him. For a man in moderate circumstances—a practicing pathologist and a millionaire collector are seldom found in one skin—the quandary seemed hopeless. But Dr. Leary has solved knottier problems. Over the years he has accumulated a surprising number of fine etchings and original drawings. There is no doubt that the exquisite craftsmanship and meticulous technic of the etcher are particularly congenial to Dr. Leary's temperament. There are three Whistlers over his desk, including the beautifully detailed study of a man's hand. There's a small Rembrandt too and an original Albrecht Durer, the somber Adam and Eve. Of more recent vintage are a Zorn, a Timothy Coles wood block and a strikingly effective drawing, *Street Scene in Sienna,* by Joseph Pennell. If, amazed at such treasures that might well grace a museum, one seeks explanation, the doctor is caught between pride and ruefulness.

"Oh I've had a lot of fun collecting these prints. A friend of mine, Abe Weber—used to be assistant district attorney—and I would go down to New York together and look at five million dollars' worth of art. Then we'd spend five dollars, or maybe 25 if we were really flush, and come home jubilant. That Durer for example. It was cut just a bit at the top and bottom, and if you look closely in the center you'll see a mark from hanging on the line to dry. There's the reason I could afford it . . . What do you think of my Rubens drawing?" pointing out a magnificently voluptuous figure over the dining room fireplace. "You know the critics are right. Pieter Paul didn't paint flesh, he *made* it." Dr. Leary's an expert; he knows flesh too.

Each little masterpiece is lovingly framed to point up its beauty, save for one memento of the etcher's craft, a delicately incised copperplate of the *Rape of Proserpine* set into the stone above the fireplace. Indeed the whole dignified old house with its wide halls and spacious rooms is furnished with the treasures of a family's heritage and lifetime. There are worn and glowing Oriental rugs. "We all like them so much they've even overflowed into the bathroom," the doctor matter-of-factly observes. "And you should inspect the Japanese prints we've hung there too. They require space for their own individuality—no mixing with occidental decorations.

"We've lived here, let's see, well over 40 years. We recently celebrated our fiftieth anniversary, and we were having our second baby when we moved in. My Better Half was in the hospital, I was here with an army of workmen putting in quarter sawed oak floors and other improvements. The house had wide boards for flooring and there are the marks of the adze on the basement beams. Probably about 110 years old they tell me. It's served us well, and now the roof's spread over my son's family too. Had plenty to work with in remodelling."

The big yard with its spreading linden trees has room for the grandchildren's swings and playhouse and pets. It has a corner too for Dr. Leary's prized mountain laurel that he coaxed into flourishing despite the wiseacres' remarks that it just wouldn't survive Boston's dust and severe climate, not to mention icy blasts from Jamaica Pond. The doctor's brown eyes sparkle with pleasure as he recounts his stubborn struggle. "I started it in a deep dugout that I boarded up with cypress. Did considerable damage to a fine ash with all my excavating too. But that was a tough tree, typical Boston native, and after 30, 40 years of struggle, it's coming nicely. And I've got my mountain laurel. Color in a garden is something I prize—that's why I love azaleas. And dahlias—not those overgrown soup plate affairs you see in exhibitions, but the

small hardy dahlias that bloom and bloom late into the fall." He sighed a little sadly. "I always enjoyed gardening, digging elbow-deep into good plain earth, kept at it when I had to sit ignominiously on a foam rubber cushion! Can't even do that now; have to let George do it."

It's clear that's never been the doctor's way; he resents being immobilized after a very active life. "Nailed to the mast," as he expresses it. And even more colorfully: "Three years ago I was 60 and full of pep and ginger; now I'm 81 and a crock." But he has neither relinquished his professional interests, nor forgotten the accumulated knowledge of a lifetime. He is still in possession of a keen mind perfectly capable of evaluating what's being done and what he himself has done. The only detraction is his innate modesty, and that's been with him from youth. So to his own chronicle of what he finds significant his colleagues and students are eager to add. First on his own list, chronologically speaking, is his study of the earliest lesions of rheumatic endocarditis. He maintains that his first findings were purely accidental—unaccountable growths disclosed in the autopsies of accident victims. One was the body of a boy run over by a streetcar. The puzzling growths that challenged Dr. Leary's inquiring mind were preceded verrucae, and have been made the basis of much fruitful study. A chance discovery? Hardly, for like other apparently casual developments, it was rooted in conscientious, painstaking routine coupled with unflagging intellectual curiosity—two of the finest ingredients of the true scientific attitude.

The great Norwegian-American doctor, Ludvig Hektoen, was particularly impressed by Leary's work on the lesions of rheumatic endocarditis, and saw to it that grants were obtained to make further study possible.

Leary's work on alcoholism has been mentioned, and his own deprecatory attitude. Concerning his work with subdural or intradural hemorrhages, however, he is enthusiastic. He has, over the years, made clear to practitioners the pathology of such conditions and the immense value of exploratory trephinement. These studies too grew out of his work as medical examiner. In the doctor's own words (from a reprint from the *Archives of Pathology*): "The Massachusetts medicolegal system gives exclusive opportunity to medical examiners to investigate the causes of death supposed to be due to violence. Because of the frequency of subdural hemorrhages, which in some years made up 10 per cent of intracranial hemorrhages in my service, I reported in 1934 a series of 50 cases. This series covered the gamut of changes which arise following escape of blood into the subdural space and made it possible to follow the evolution of the process in its various stages from the beginning to the end result, i.e., from fluid blood to complete organization. A series of cases seen since confirms the conclusions arrived at from study of the first series.

"Because of the peculiar character of the attempt to organize a subdural hemorrhage (with activities in this respect limited to the relatively avascular dura, while the highly vascularized arachnoid remains inactive), a study was made of the subdural space and its linings. This study disclosed that the subdural space is not a serous space . . ."

The study continues with its discussion of the lesions dependent on subdural hemorrhages and a classification into five groups, each marking a stage in the aging and progress of the hematoma. But Dr. Leary was not content to distill his wisdom into a few pages for the solemn *Archives of Pathology,* nor even to confine it to formal lectures. He was given the latter opportunity when the New York Academy of Medicine invited him to present the Ludwig Kast opening lecture, and to participate in The Graduate Fortnight with a paper on head injuries with special emphasis on subdural hemorrhage. He has spoken at the California Academy of Medicine also, where matters are handled with characteristic flair and everybody dons evening dress for the occasion. "They pay a fee; it should be festive!"

But the doctor was convinced that ordinary general practitioners should know these things too, and New England practitioners at least were going to know them if he had to tell them himself. And he did! Accompanied by a neurosurgeon, John S. Hodgson, and a psychiatrist, his ex-student and brilliant colleague in forensic medicine, Abraham Myerson, he barnstormed through the New England states making one-

day stands and demonstrating his conclusions as to what brain injuries really are, with a blackboard and two large cans of brains!

Such exuberant pioneering was a welcome change from the constant pressure of crowded days in Boston. "Not that I coudn't stand the pace. I had vim and vigor enough in those days. Fatigue is a strange thing—I remember once I went to the office of Harvey Cushing, the famous brain surgeon. On this occasion I had a pituitary I wanted him to take a look at, all complete in its cuplike cradle of bone as I'd lifted it from the autopsy table. As I sat there waiting, the inner door opened and there in a dismal, sickly-hued, greenish operating gown stood a pallid, shambling wreck of a man. I blinked, shook my head, not believing that pitiful apparition was indeed the great Dr. Cushing. That's what brain surgery could do to even its most brilliant exponent—operating and then watching, waiting, for all that interminable hour lest any single drop of blood warn by its very presence of imminent hemorrhage and disaster.

"I was choked with pity, I tried to leave, but he flapped a hand toward me, staggered to a chair and fell into it. Then he lighted a cigarette, and while I watched he gradually took on his normal semblance. That's the strain of his kind of surgery, the sum of those nerve-wracking hours of operating plus that last almost unendurable vigil." Dr. Leary's dark eyes clouded with memory and his sensitive face reflected the compassion that had filled him for his friend.

As it happens Dr. Leary's wife, Olga, was a Cushing before her marriage, but of an entirely different branch of the family. Her father, Earnest Watson Cushing, was also a professor at Tufts and a distinguished gynecologist. He had his own hospital built on the site where the New England Baptist Hospital now stands. His daughter, an enterprising young woman, not only took her medical degree at Tufts but caught the attention of the professor of pathology and bacteriology. Dr. Leary recalls the circumstances with a twinkle. "Why she was willing to do anything—help with the animals, clean up the lab, run through a series of tests. And was she good at it!" That recollection of her husband's offers but a faint foreshadowing of the competence and versatility Dr. Olga Leary has never ceased to demonstrate. She became assistant professor of pathology at Tufts, and when her husband finally left his post there to devote all his time to the job of medical examiner, she set up the Leary Laboratory on Bay State Road. There, the many medical friends and one-time students who had come to depend on having laboratory tests and analyses done under Leary supervision at Tufts, were able to bring their specimens and samples. Conveniently located in the medical center of Boston, the laboratory turns to the street a staid dwelling-house facade and opens its big rear windows to a view of the Charles Basin. In between there are rooms filled to the ceiling with cages of test animals, apparatus of all kinds, carefully indexed files, and serious young technicians in white coats circulating purposefully from sink to microscope. "Dr. Olga" brought along her classmate, Dr. Dunbar, when she set up the laboratory, and the rest of the personnel was recruited from Tufts and trained in the skilled technics and high standards of the Leary tradition. From the very beginning they've been swamped with work, and have filled a need that would not have been met.

Such a demanding professional life would seem more than sufficient for any one woman, and Dr. Olga Leary, though quick-moving and direct, is slight, delicately made. Somehow she has found time and strength for three children, a son who contributes to the wonders performed by electronic "human brains" in the research division of Massachusetts Institute of Technology, just across the Charles from the Leary Laboratory; and two daughters, both of them fullfledged doctors. No wonder a guest, upon being introduced to Olga II at a party recently, hovered between awe and diffidence, finally murmured, "Tell me, are you one of the Fabulous Learys?"

Actually Olga is pathologist at the Soldiers' Home in Chelsea and part time assistant to her mother in the Leary Laboratory—when she's not crocheting, entertaining, or going to parties like any other charming, less learned young woman.

Deborah too followed the family pattern, acquired not only a degree from the Yale Medical

School but a husband as well who is an associate professor of medicine in the school. After shifts about the country with him and time out for his war service she is returning to the practice of obstetrics and gynecology, her grandfather Cushing's field.

The elder Learys are too busy with their own professional interests to lean back in dewy-eyed pride, but surely the feeling is rightfully theirs. And something of the doctor's proud and loving regard for his partner of more than 50 years warms his voice as he speaks of "My Better Half." A tender, mock-solemn gaiety suffuses the trite words, and one suddenly realizes that in addition to so many other qualities Timothy Leary also has that inimitable Irish charm!

Today Dr. Timothy Leary's professional interests center around atherosclerosis and the effects of cholesterol in the human diet. He is preeminently qualified to discuss the subject as his many contributions to its literature bear witness. The American Medical Association presented him with its silver medal for work in that field. Frequent papers reprinted from the *Archives of Pathology* embody his clear thinking and far-reaching conclusions under such prosaic titles as "Crystalline ester cholesterol" and "Adult cortical renal tumors." He has indeed dealt with the subject brilliantly and exhaustively. But here's the fabulous Leary touch—he wrote his first paper on the subject at the age of 62! It is in the last 20 years that he has become an authority.

Leisure, even though it be enforced by a bad back, is conducive to philosophizing, which, coupled with Dr. Leary's background of experience and scientific knowledge, adds up to the kind of thinking we so need and seldom find. Meticulously dressed in a dark brown suit and small-patterned harmonizing tie, the doctor sits in a corner of the living room dominated by a marble bust of Athena. His upright posture is imposed by a strong will quite as much as by that "infernal leather harness." Lounging, mental or physical, has no place in the Leary regimen. Musing is a different matter altogether.

"You see this preoccupation with cholesterol beckons one on toward all sorts of possibilities. The sterols are tremendously important; they're the agents for good or ill in the human body. They're responsible for sex, for the cortical adrenal hormones. That's why women are bombproof for coronary disease up to the menopause. Their hormones eat up the excess cholesterol. But that apparent indication for therapy is deceptive; give men too much stilbestrol and they just develop diminutive breasts! Oh the sterols are fine, if they're right and in balance.

"Sterols are present in every living cell—and they are never found outside of living cells. They are symbols of life; perhaps they are a manifestation of the primordial stream of life, for their make-up suggests they come to us from the sea, our source and origin . . ."

Living has given much to Dr. Leary, and out of the brilliance of his mind and the integrity of his character he has given much to life. His own eyes rest most frequently and appreciatively on the beautiful etchings he has collected, but a visitor's gaze is drawn and held by an illuminated scroll hung where the light is rather poor. It reads:

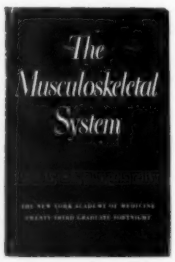
"Timothy Leary, M.D.

"Pathologist, Teacher, Medical Examiner in Suffolk County from 1908 to 1950, whose career and unswerving devotion to duty has always been an inspiration and example to his pupils and associates—this scroll is presented by his fellow members of the Massachusetts Medico-Legal Society. October 18, 1950."

LUCILE C. DEINARD

THE MEDICAL *Bookman*

THE MUSCULOSKELETAL SYSTEM*



In this symposium are presented the formal lectures which were the principal features of the graduate fortnight which has become an established event among the many activities of the New York Academy of Medicine. The program also included panel discussions, clinics, exhibits, motion pictures and televised surgical operations.

Following discussions on the basic structure and chemical nature of connective tissue, come reviews of physiology, biochemistry and pathology as they concern muscles, bones and the blood. The more clinical chapters deal with the effects of cortisone and ACTH, rheumatoid arthritis, gout, the collagen diseases, nonarticular rheumatism, pyogenic arthritis, tuberculosis and tumors of bones and joints, and aseptic necrosis of bone. Each of the authors is distinguished in the field he discusses.

The introductory lectures are up to date with the results of most recent research, such as the inhibiting effect of cortisone on the spreading action of hyaluronidase and the specific effect of vitamin C in synthesizing and maintaining scar tissue. The functions of mucopolysaccharides in connective tissue are considered editorially with elucidation of various views. Most of the problems of connective tissue chemistry are still to be solved. Dr. Joseph L. Lilienthal, Jr. of Johns Hopkins reviews recent advances in the physiology of muscle and shows how chemical changes may result in muscular weakness or cramps.

The chapter by Dr. Donald McEachern of Montreal on diseases and disorders of muscle function covers myotonia, myasthenia, thyroidal muscular disorders, periodic paralysis and dystrophies. Myotonia is abolished by cortisone and returns when the drug is discontinued. Myasthenia gravis appears to be an endocrine or metabolic disorder. Removal of the thymus benefited many young patients. The adrenocortical steroids have the effect of shrinking the thymus but both ACTH and cortisone seemed to make the myasthenic patient worse during the period of administration. The author seems to hint that wheat germ may be of value in progressive muscular dystrophy but he deprecates the confused writings on the subject.

A profound discussion of metabolism in bone presents many unsolved problems, and Dr. I. Snapper's consideration of metabolic bone diseases reveals the extent to which our knowledge of bone metabolism has been helpful in bone diseases. Equally profound is the review by Dr. Marcy L. Sussman of skeletal changes associated with diseases of the blood. He concludes that there is a change in the metabolic and enzyme systems in primary blood disorders, specific for such diseases. These changes alter the protein substrate available for bone formation and the physicochemical conditions for calcium precipitation.

Dr. Joseph P. Bunim has reviewed the status of therapy with cortisone and ACTH and offers great encouragement in the treatment of a variety of rheumatic conditions.

The remaining essays are most practical, but unfortunately the book lacks an adequate index which would have enhanced the utility of the material.

T. E. B.

(Continued on page A-50)

*THE MUSCULOSKELETAL SYSTEM, TWENTY-THIRD GRADUATE FORTNIGHT OF THE NEW YORK ACADEMY OF MEDICINE. EDITED BY MAHLON ASHFORD, M.D. 368 PAGES WITH 103 FIGURES. 1952, THE MACMILLAN COMPANY, NEW YORK. $6.50.